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Toxicology and b..



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~~aromatic~~
~~hydrocarbons~~

1. industrial hygiene.

2. benzene

3. polycyclic aromatic hydrocarbons

4. solvents 5. fuels

6. lubricants

TLMS



TOXICOLOGY AND BIOCHEMISTRY
OF AROMATIC HYDROCARBONS

~~H.C.~~

H.C.

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ON
TOXIC AGENTS

EDITED BY

ETHEL BROWNING, M.D.

FORMERLY H.M. MEDICAL INSPECTOR OF FACTORIES
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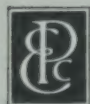
TOXICOLOGY AND BIOCHEMISTRY OF AROMATIC HYDROCARBONS

BY

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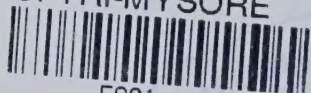
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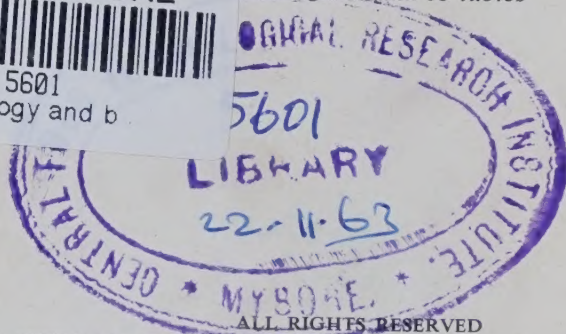
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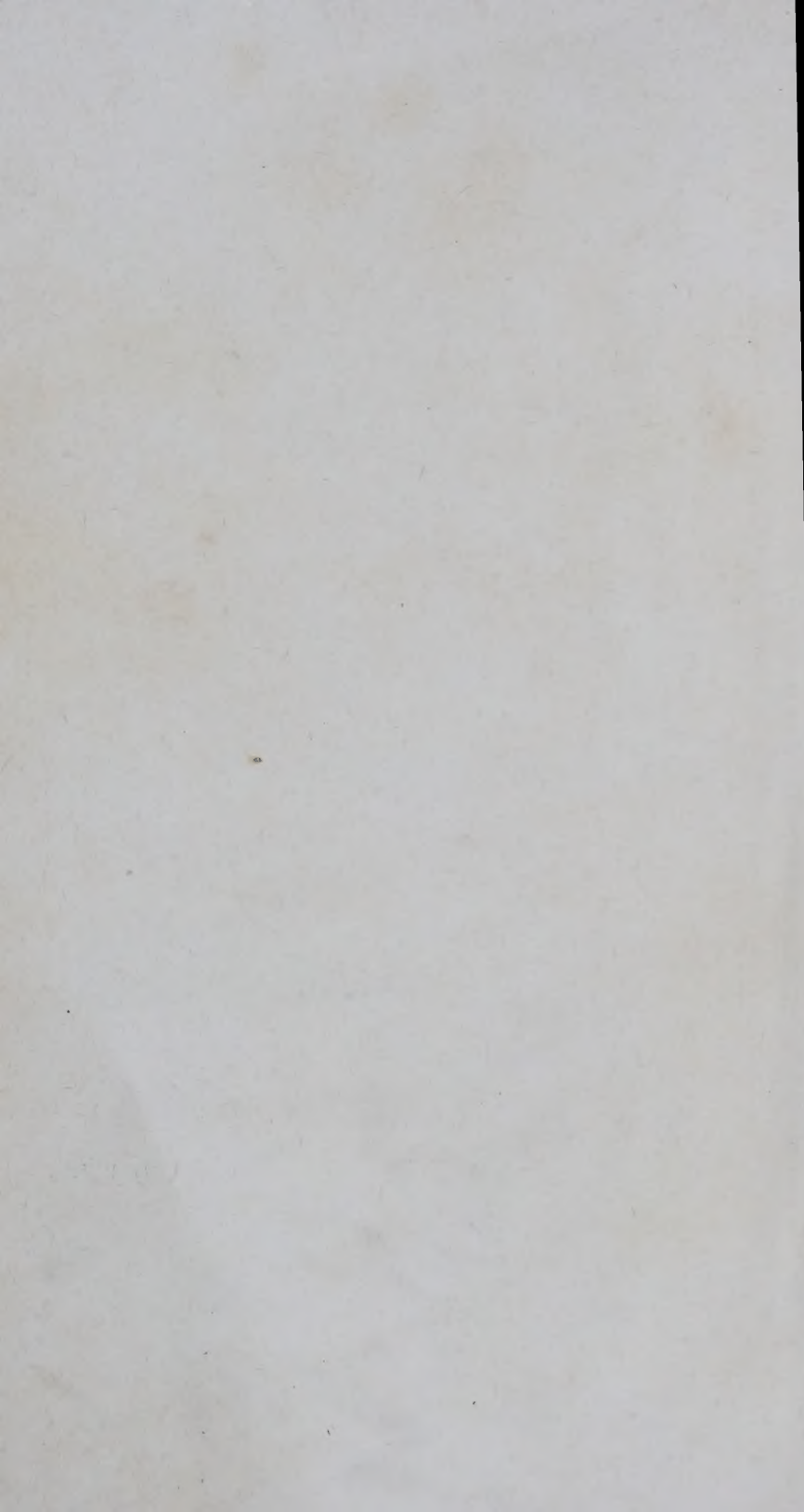
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To my wife



Part I

GENERAL CONSIDERATIONS

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Preface

The purpose of this book is to assemble in one volume information primarily of interest to the physician, industrial hygienist and toxicologist, who are concerned with the prevention, detection and treatment of exposure to the aromatic hydrocarbons of industrial importance. In addition to the toxicology and biochemistry, the physical properties, uses, probable modes of contact, and methods of analysis are discussed since these topics are important in the prevention and evaluation of exposure to chemicals. The detection of incipient or sub-clinical toxicity are of primary interest to the industrial physician and toxicologist. Of interest primarily to the physician is the discussion of the replacement and periodic medical examinations and the treatment of exposure to the aromatic hydrocarbons.

The book is divided into two parts. Part I is concerned with an over-all treatment of the subject from the point of view of basic chemistry, nomenclature, sources, uses, economic importance, analysis, toxicology, biochemistry and prevention, detection and treatment of exposure to the aromatic hydrocarbons. Part II consists of detailed discussions of 20 individual aromatic hydrocarbons of industrial importance which are treated under the same general headings as those used in Part I. This is followed by a discussion of carcinogenesis in the chapter on the polycyclic aromatic hydrocarbons. The final chapter is concerned with aromatic hydrocarbon mixtures encountered in industry -- the solvents, fuels and lubricants.

The information included in the book has been drawn from numerous publications in the field of industrial toxicology, industrial hygiene and biochemistry. Particular attention was given to recent information which has not yet been included in books on toxicology or industrial hygiene. Statements made and data presented are documented to permit the reader to find the original sources for further information. The literature has been covered through September, 1959.

Acknowledgments

is with pleasure and a feeling of gratitude that I acknowledge my indebtedness to the many people who have contributed directly or indirectly to this book.

I wish first of all to express my admiration and appreciation to the many investigators who conducted the research described in this small volume. Many of the names will be found in the bibliography and in the footnotes to the tables and figures.

I would be remiss if I did not mention some individuals who have made outstanding contributions to the field of the toxicology and metabolism of the aromatic hydrocarbons. It has been a privilege to read and summarize the studies reported in the literature by Dr. René Fabre, Dr. René Truhaut and co-workers of France, Dr. R. T. Williams and co-workers, Dr. H. V. Thorpe, Dr. L. Young and Dr. E. Boyland and co-workers of England, Dr. J. Teisinger and co-workers of Czechoslovakia and Dr. I. Berenblum of Israel, and Dr. E. Grandjean of Switzerland. The contributors in the United States are scientists to whom I am privileged to know personally. Among them are Dr. J. B. Deichmann, Dr. Henry Smyth, Jr., Dr. Charles Carpenter, Dr. Don Irish, Mr. V. K. Rowe, Dr. Howard Spencer and co-workers, Dr. C. H. Hine, Dr. Joseph Svrbely, Dr. W. F. Oettingen and Dr. C. Boyd Shaffer.

I am grateful to the Esso Research and Engineering Co. for giving me the opportunity to carry out my own research, much of which is described in this book. This was made possible

through the efforts, support and encouragement of Dr. R. Eckardt, Director of the Medical Research Division, and W. J. Sweeney, Vice-President of the Esso Research and Engineering Co. These studies were conducted with the assistance of Mrs. D. B. Ahlstrom of Rutgers University whom I owe a special debt of gratitude. I am also grateful to J. A. Allison, Director of the Bureau of Biological Research, Rutgers University, for providing the facilities, the freedom and climate conducive to basic research.

I wish to thank Dr. Ethel Browning and the Elsevier Publishing Company for presenting me with the opportunity to write this book because it is doubtful if the task would have been undertaken without this initial impulse.

In the actual preparation of the manuscript I am above all indebted to my wife who gave not only moral support but expert editorial and secretarial assistance, in addition to filing the numerous reprints and journal articles collected in the past 7 years. To my daughters, Patty, Peggy and Nicky, I extend my appreciation for their forbearance as well as their actual assistance (commensurate with their ages) offered during the time the manuscript was in preparation.

For the photographs reproduced here, my thanks are due Mr. Jack Carrar and staff, particularly Mr. Dennis Crow, of the Products Research Division, Esso Research and Engineering Co. I wish also to thank individuals, the companies and the publishers for contributing photographs and other descriptive material used in this book.

It is a pleasure to acknowledge the constructive criticism and substantial help of Dr. B. E. Bennison, Assistant Director, M. N. Hendricks, of the Industrial Hygiene Section, Mrs. L. McTurk, of the Information Section, and Mrs. Emma Warren, librarian, of the Medical Research Division of the Esso Research and Engineering Co.

To Mrs. Ann O'Connell and her competent staff of stenographers and typists I owe my thanks for the typing of the

manuscript. Mrs. Maryann V. Veit was responsible for typing and collating the final copy in addition to typing the major part of the first draft. Her efficiency, diligence and skill in reading handwriting are greatly appreciated.

I am guilty of editorial sins of omission or commission, or of adapting or adopting where I should have obtained permission. I trust that these will be recognized as unintentional and I offer my apologies.

Princeton, N.J.

August 1960

HORACE W. GERARDE, M.D., Ph.D.

definition, nomenclature, and classification of aromatic hydrocarbons

DEFINITION OF AROMATIC HYDROCARBON

The term 'aromatic' is derived from the fact that the earliest known representatives of the class of 'aromatic compounds' were resins, oils, and balsams distinguished by a marked aromatic odor. The terms 'aromatic', 'arene', or 'benzenoid' are applied to all substances containing one or more 'benzene nucleus' or 'benzene residue'. This refers to a cyclic arrangement of carbon and hydrogen atoms characteristic of benzene, the simplest example of an aromatic hydrocarbon, consisting of a hexagonal symmetrical ring of six equivalent CH groups.

The elucidation of the structural formula of benzene is a fascinating episode in the history of organic chemistry. The structural formulas for benzene shown in Fig. 1 were first proposed by Kekulé in 1865. This masterly revelation reconciled the old aliphatic theory with the unusual chemical properties of benzene. Among some of the things it explained were the 'anomalous' degree of unsaturation, the chemical stability, and the equivalence of the 6 hydrogen atoms in the molecule. The present day view of the structure of benzene is that the hydrocarbon is a so-called *resonance hybrid* receiving equal contributions from the two cyclohexatriene structures, H and D, shown in Fig. 1 (Wheland, G. W., 1949). Benzene is considered to have a structure which is not identical with either H or D but halfway between them. This is described graphically by the structure M

in which the double-headed arrow \longleftrightarrow representing resonance is to be distinguished from the pair of arrows \rightleftharpoons representing chemical equilibrium. All benzene molecules always possess a single hybrid structure which is intermediate between H and D.

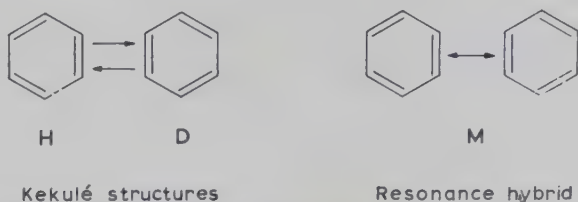


Fig. 1. Kekulé formulas and resonance hybrid structure of benzene.

Just as the mule is a hybrid between a horse and a donkey and is a single kind of animal, M in Fig. 1 represents the 'benzene mule' between H and D. A single molecule of benzene does not have formula H part of the time and formula D the rest of the time. To continue with the biological analogy, a mule is not a horse part of the time and a donkey the rest of the time. The hypothetical 'benzene mule' is possible because the double bonds of the benzene rings in H and D are free to oscillate between the two possible positions. The bonds represent electrons which can be re-distributed around the carbon atoms in the hexagonal plane without any movement of the atomic centers.

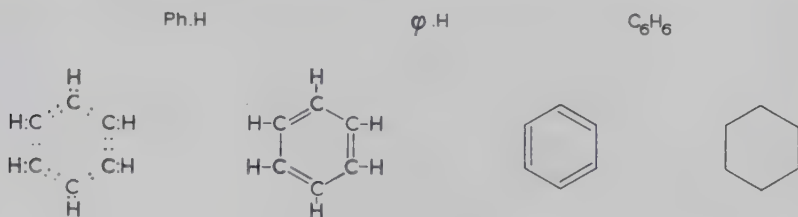


Fig. 2. Graphic representations of benzene.

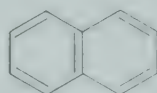
For convenience in writing, the benzene ring is ordinarily represented by a hexagon, with alternating double bonds, but it may be represented by the other graphic forms shown in Fig. 2 and the molecular model shown in Fig. 8, page 9.

NOMENCLATURE AND CLASSIFICATION OF AROMATIC HYDROCARBONS

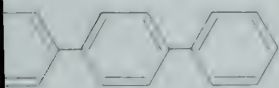
Aromatic hydrocarbons are classified according to the number of benzene rings and the type of linkage or attachment between the rings in the molecule. The number of rings is designated by Greek prefixes followed by the term 'aromatic' or 'nuclear'. The benzene rings may be joined or attached by single bonds as in diphenyl (biphenyl), terphenyl, etc. or they may be 'fused' or 'condensed' so that two carbon atoms are shared between two benzene rings as illustrated by naphthalene. The polycyclic aromatic or polynuclear hydrocarbons are classified as linear or angular, illustrated by anthracene and phenanthrene, respectively. These conventions of naming are shown in Fig. 3.



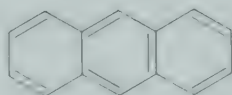
Diphenyl
(Biphenyl)
(Condensed)
aromatic or
dinuclear



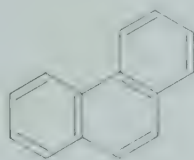
Naphthalene
(Condensed or fused)
aromatic or
dinuclear



Triphenyl
(Condensed)
aromatic or
trinuclear



Anthracene
(Linear condensed)
aromatic or
trinuclear



Phenanthrene
(Angular condensed)
aromatic or
trinuclear

Fig. 3. Naming of multiple ringed aromatic hydrocarbons.

The chemical groups derived from aromatic hydrocarbons by removal of one hydrogen atom are called *aryl* groups, i.e., *phenyl* from benzene, *naphthyl* from naphthalene etc. *Arylene* refers to a bivalent radical derived from an aromatic hydrocarbon by removal of a hydrogen atom from each of two carbon atoms of the nucleus, i.e., *phenylene*, *naphthylene*.

The positions of substituting groups on the various rings are usually indicated by a system of numbering or by the use of the Greek alphabet for small symmetrical molecules. In the benzene series of hydrocarbons, disubstitution positions are often indicated by the terms *ortho* (abbreviated *o*) for the 1,2-positions; *meta* (abbreviated *m*) for the 1,3-positions; and *para* (abbreviated *p*) for the 1,4-positions. In cases of trisubstitution, the terms vicinal (*vic*), asymmetrical (*as*), and symmetrical (*sym*) are often employed to indicate the positions 1,2,3; 1,3,4; and 1,3,5, respectively (see Fig. 4).

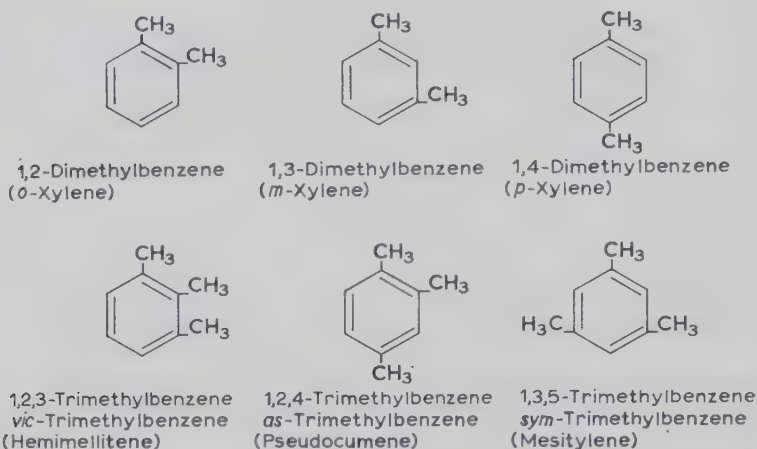
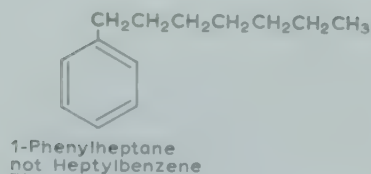
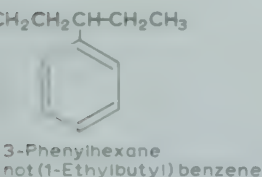
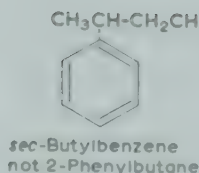
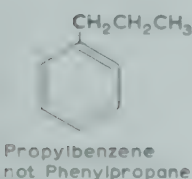


Fig. 4. Naming of di- and tri-substitution products of benzene.

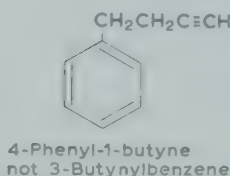
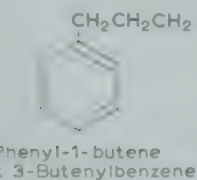
Mono-aliphatic derivatives of benzene are named by: (1) prefixing the radical name denoting the side chain to benzene; (2) prefixing the radical *phenyl* to the name of the aliphatic hydrocarbon. For saturated side chains, the 'largest index compound' is named as the 'parent'. For unsaturated side chains, the aliphatic hydrocarbon residue is regarded as the 'parent'. These conventions of naming are illustrated in Fig. 5.

Naphthalene yields only two mono-substitution products which are known as the *alpha* and *beta* forms. The orientation of naphthalene derivatives is indicated by systems shown in Fig. 6. The 4,5 and 1,8 positions are often called the *peri* positions.

Saturated side chain



Unsaturated side chain



Exceptions

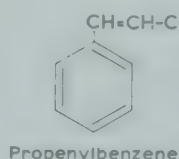
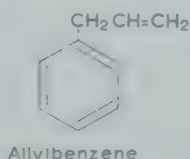
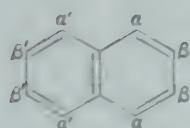
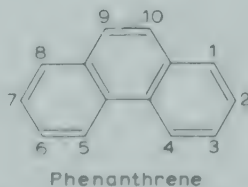
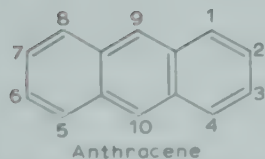
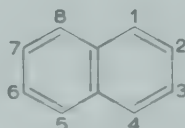


Fig. 5. Naming of mono-alkyl derivatives of benzene.



Naphthalene



Naming and numbering of carbons in naphthalene, anthracene and phenanthrene.

tions. The usual method for naming anthracene and phenanthrene derivatives is also shown in Fig. 6. The principal aromatic hydrocarbon ring systems are shown in Fig. 7. Molecular mo

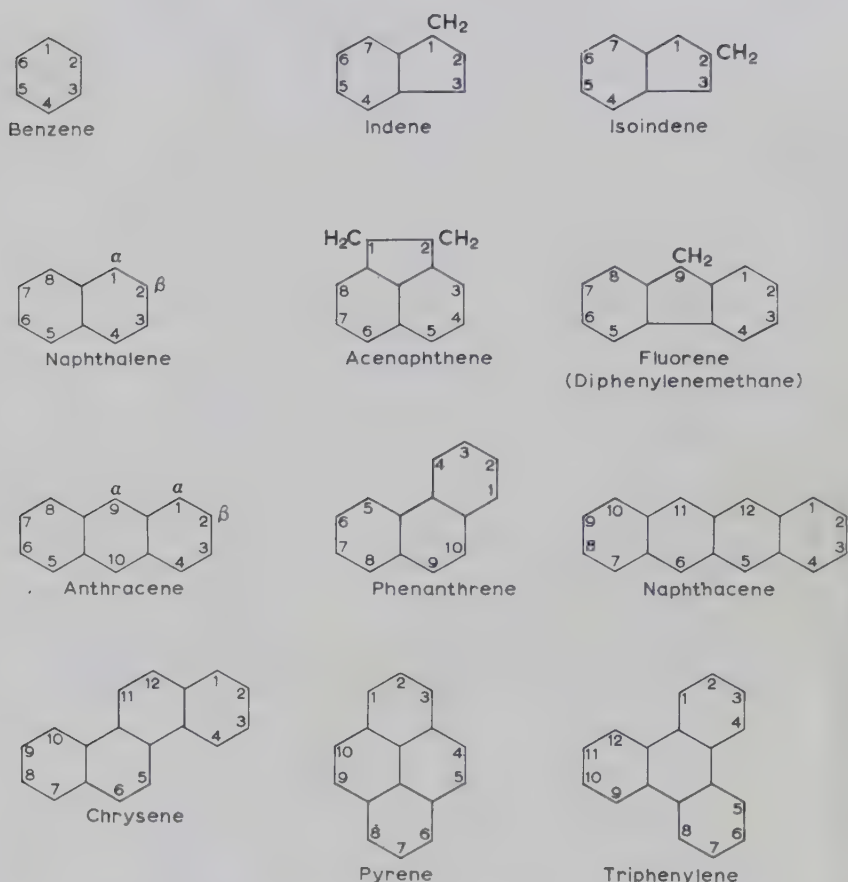
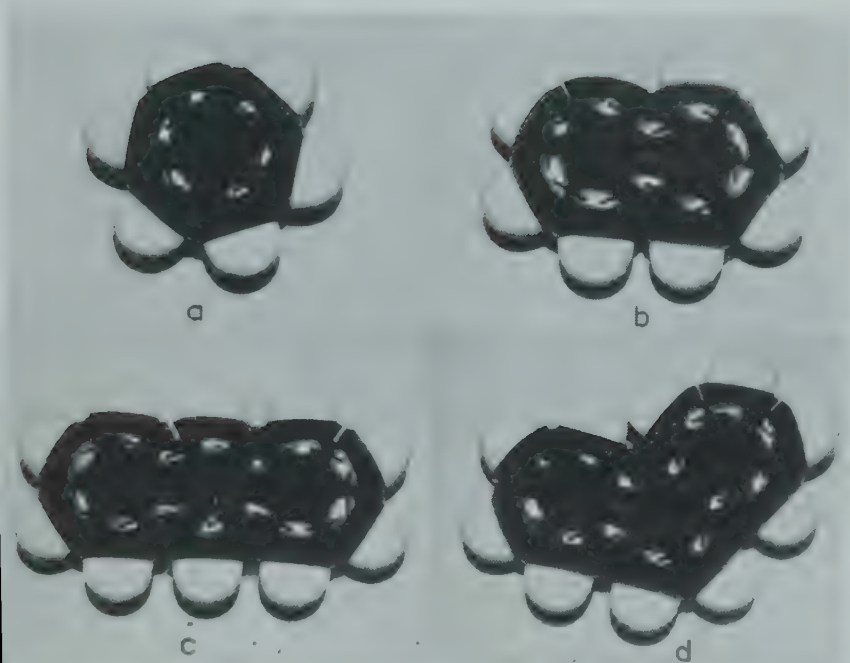


Fig. 7. Principal aromatic hydrocarbon ring systems.

depicting benzene, naphthalene, anthracene and phenanthrene are shown in Fig. 8.



8. Molecular models of aromatic hydrocarbons (according to Stuart Briegleb; magnification $1.5 \cdot 10^8$) a. Benzene; b. Naphthalene; c. Anthracene; d. Phenanthrene.

The economic importance, sources, and uses aromatic hydrocarbons

THE ECONOMIC IMPORTANCE OF THE AROMATIC HYDROCARBONS

The industrial use of the aromatic hydrocarbons had its beginning about 1823 when *coal tar naphtha* made in the London gas plants was found to be an excellent solvent for rubber. This hydrocarbon mixture was used to produce the first waterproof cloth and was also found useful for preparing varnish and for burning in lamps. In 1825, Michael Faraday first isolated benzene, one of the principal constituents of *coal tar naphtha*, from an oily condensate deposited from compressed illuminating gas. The principal constituents of *coal tar naphtha*, benzene, toluene and xylene (BTX), are three of the most important organic chemicals in industry.

The discovery by W. H. Perkins, in 1856, of a method for producing synthetic aniline dyes from coal tar products gave further impetus to the use of aromatic hydrocarbons in industry. Rapid progress followed in the field of synthetic chemistry based on aromatic hydrocarbons (benzene, toluene, naphthalene, anthracene) as starting materials for synthesis of dyes, drugs, perfumes, flavors and disinfectants. The stress of World War I created great needs for benzene and toluene for the synthesis of explosives, picric acid and trinitrotoluene (TNT).

Supplies of toluene from coal tar for the synthesis of trinitrotoluene proved to be inadequate to meet the demands. Before

World War I the Germans had succeeded in separating aromatic hydrocarbons from Borneo crude oil and, during the war, had diverted this supply for use in making explosives. The United States also made explosives from the aromatic hydrocarbons separated from California crude.

At the end of World War I, the accumulated war stock of benzene was diverted to blending in anti-knock motor fuel. Motor benzol consumption grew to a hundred million gallons annually (Haynes, W., 1936). Benzene also found new applications as a solvent for artificial leather, plastics and lacquers. World War II created phenomenal demands for the aromatic hydrocarbons for aviation fuels, synthetic rubber, plastics, protective coatings, solvents, detergents, and other organic chemicals. The demand for aromatic hydrocarbons has continued in the post-war period as shown in Table 1. In 1957 69% of the total

TABLE 1

POST-WAR GROWTH OF DEMAND FOR AROMATIC HYDROCARBONS*
(Millions of gallons)

Year	Benzene	Toluene	Xylene	BTX total
1945	218	200	55.9	474
1946	165	34	44.9	244
1947	187	60	41.4	289
1948	185	84	61.1	330
1949	158	82	57.6	298
1950	204	84	71.9	360
1951	225	102	75.7	403
1952	244	105	71.8	421
1953	261	157	113.5	532
1954	289	139	110.1	538
1955	315	150	107.9	573
1956	350	165	136.3	651
1957	347	180	143	670

*Compiled from Hansen, N. and Groves, D. (1959).

aromatic hydrocarbon supply in the United States was derived from petroleum and 23.2% came from iron, steel, and coke producers, imports accounting for 7.8%. Table 2 shows

TABLE 2
PRODUCTION OF AROMATIC HYDROCARBONS
IN WESTERN EUROPE (ESTIMATED) AND U.S.A. (ACTUAL)*
(millions of pounds)

<i>Hydrocarbon</i>	<i>France</i>	<i>Italy</i>	<i>Western Germany</i>	<i>U.K.</i>	<i>Others</i>	<i>U.S.</i>
Benzene	142	50	1200	—	130	243
Toluene	—	11	65	—	4	143
Xylene	16	11	65	—	7	92
Styrene	—	30	—	100	—	116
Ethylbenzene	—	—	—	—	—	116
Naphthalene	—	—	—	—	—	42

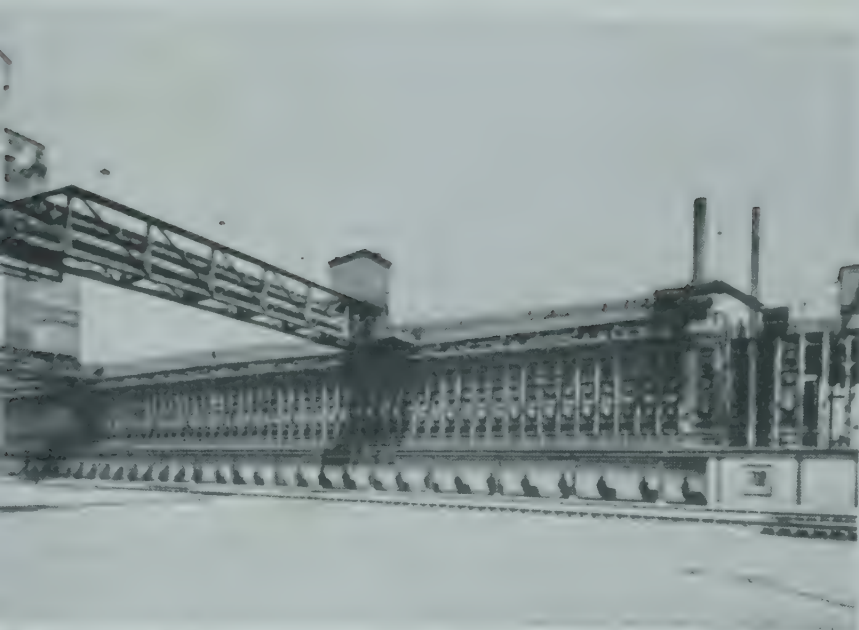
* Compiled from U.S. Tariff Commission Report No. 203 (1957) Katzen, R. (1958).

estimated production of the principal aromatic hydrocarbons in Western Europe and the actual output in the United States for 1957.

SOURCES OF AROMATIC HYDROCARBONS

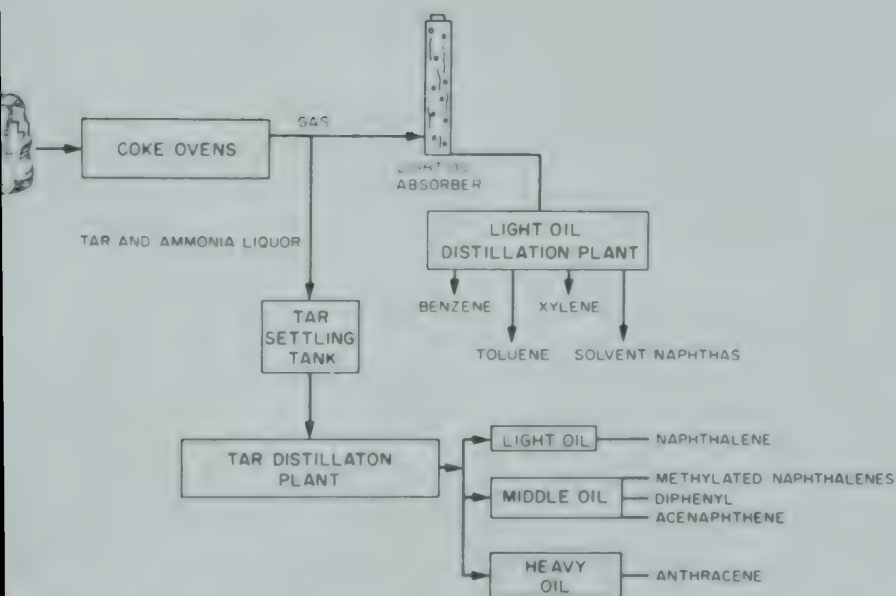
Coal

The heating of bituminous coal at temperatures in the range 1000-1300°F in a retort without access to air converts it into coke, coal gas, and a condensate consisting of a black viscous tar and a water layer containing ammonia (Fig. 9). In refining the gas is passed through tar and ammonia scrubbers and then through oil-absorption tanks for absorption of a *light oil*. The light-oil fraction contains benzene, toluene and xylene (crude



9. Battery of Koppers-Becker underjet coke ovens.

(Courtesy Koppers Co., Inc., U.S.A.).



10. Schematic diagram for manufacture of aromatic hydrocarbons from coal tar.

coal tar naphtha and heavy solvent naphtha). The yield of oil is about 3.2 gallons per ton of coal. Crude 'motor benzene' consisting principally of benzene and toluene is obtained by scrubbing of coke-oven gas. The yield of coal tar is about 10% of the weight of the coal. The principal aromatic hydrocarbons present in coal tar are diphenyl, naphthalene, methyl naphthalenes, indene, acenaphthene, fluorene, chrysene, phenanthrene. Many of the hydrocarbons present in the tar are probably formed by the pyrogenic polymerization of acetylene, since this hydrocarbon when heated forms many of the products found in coal tar. Fig. 10 shows a schematic flow diagram for the manufacture and recovery of aromatic hydrocarbons from coal.

Petroleum

Aromatic hydrocarbons are produced from petroleum by the following basic methods:

- (1) Removal from the crude oil by fractional distillation, solvent extraction or crystallization.
- (2) Alkylation of lower aromatic hydrocarbons.
- (3) Catalytic reforming.

Alkylation of lower aromatic hydrocarbons refers to the addition of an alkyl group to an organic compound. This is illustrated by the formation of ethylbenzene from benzene and ethylene, shown in Fig. 11.

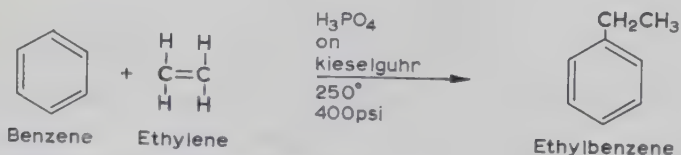


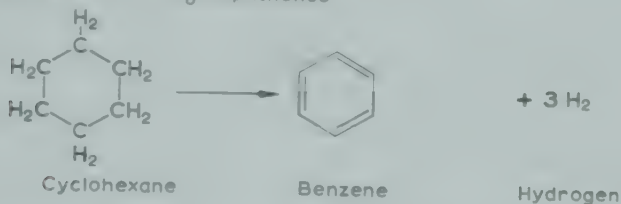
Fig. 11. Formation of ethylbenzene by alkylation.

Catalysts used in alkylation of aromatic hydrocarbons must consist of anhydrous halides of the Friedel-Crafts type, such as aluminum chloride, zirconium chloride, and boron fluoride,

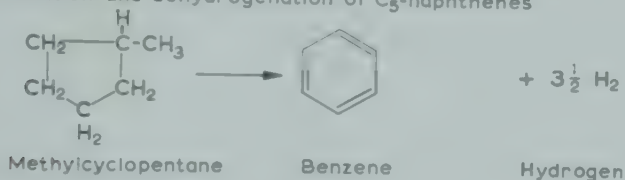
8, principally concentrated sulfuric, phosphoric acid, liquid nitrogen fluoride, and synthetic silica-alumina cracking cata-

catalytic reforming, a number of chemical reactions take place which transform hydrocarbons into aromatic hydrocarbons, as shown in Fig. 12.

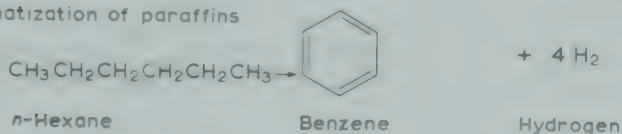
1. Dehydrogenation of C₆-naphthenes



2. Isomerization and dehydrogenation of C₅-naphthenes



3. Aromatization of paraffins



Isomerization of paraffins



Hydrocracking



Fig. 12. Reactions occurring in catalytic reforming.

reaction is generally carried out at 450-500° in the presence of molybdenum, chromium or precious metal oxide catalyst supported on alumina. By the proper choice of conditions almost any desired increase in aromatic content may be obtained. The wide variety of aromatic hydrocarbons formed

TABLE 3

COMPOSITION OF EIGHT-CARBON ATOM AROMATIC
HYDROCARBONS IN CATALYTIC REFORMATE*

<i>Hydrocarbon</i>	<i>Boiling point, °F</i>	<i>Freezing point, °F</i>	<i>Weight %, based on total C₈ aromatics</i>
Ethylbenzene	277	— 139	21.2
<i>p</i> -Xylene	281	+ 56	18.3
<i>m</i> -Xylene	282	— 54	40.4
<i>o</i> -Xylene	292	— 13	20.1

* After Earhart, H. W. *et al.* (1959).

TABLE 4

COMPOSITION OF NINE-CARBON ATOM
AROMATIC HYDROCARBONS IN CATALYTIC REFORMATE*

<i>Hydrocarbon</i>	<i>Boiling point, °F</i>	<i>Freezing point, °F</i>	<i>Weight %, based on total C₉ aromatics</i>
Isopropylbenzene	306	— 141	0.6
<i>n</i> -Propylbenzene	319	— 147	5.2
<i>m</i> -Ethyltoluene	322	— 140	17.4
<i>p</i> -Ethyltoluene	324	— 80	8.6
1,3,5-Trimethylbenzene (Mesitylene)	329	— 49	7.6
<i>o</i> -Ethyltoluene	329	— 114	9.1
1,2,4-Trimethylbenzene (Pseudocumene)	337	— 47	41.3
1,2,3-Trimethylbenzene (Hemimellitene)	349	— 14	8.2
Indane	352	—	2.0

* After Earhart, H. W., *et al.* (1959).

TABLE 5

COMPOSITION OF TEN-CARBON ATOM
AROMATIC HYDROCARBONS IN CATALYTIC REFORMAT*

Hydrocarbon	Boiling point, °F	Freezing point, °F	Weight % based on total C ₁₀ aromatics
tylbenzene	336	— 72	0.1
tylbenzene	343	— 61	0.5
tylbenzene	344	— 104	0.1
ymene	347	— 83	0.2
ylene	351	— 90	0.7
ylene	353	— 97	Trace
Diethylbenzene	358	— 119	1.6
thyl-3- <i>n</i> -propylbenzene	360		3.0
thyl-4- <i>n</i> -propylbenzene	362	— 81	2.8
tylbenzene	362	— 126	3.6
Diethylbenzene	362	— 25	2.5
Dimethyl-5-ethylbenzene	363		4.0
Diethylbenzene	363	— 46	0.8
thyl-3- <i>n</i> -propylbenzene	363	—	1.8
thylindane	367	—	3.5
thylindane	369	—	1.3
Dimethyl-2-ethylbenzene	368	— 65	4.7
Dimethyl-4-ethylbenzene	371	— 81	6.0
Dimethyl-4-ethylbenzene	374	— 89	9.6
Dimethyl-2-ethylbenzene	374	— 3	1.0
Dimethyl-3-ethylbenzene	381	—	4.1
5-Tetramethylbenzene (arene)	385	+ 175	8.0
5-Tetramethylbenzene (durene)	388	— 11	12.7
thylindane	395	—	2.9
thylindane	395	—	13.4
4-Tetramethylbenzene (pseudocumene)	401	+ 21	5.3
thylene	424	+ 176	5.8

* Earhart, H. W. *et al.* (1959).



Fig. 13. Catalytic reformer for production of aromatic hydrocarbons from petroleum. (Courtesy Esso Research and Engineering Company, U.S.)

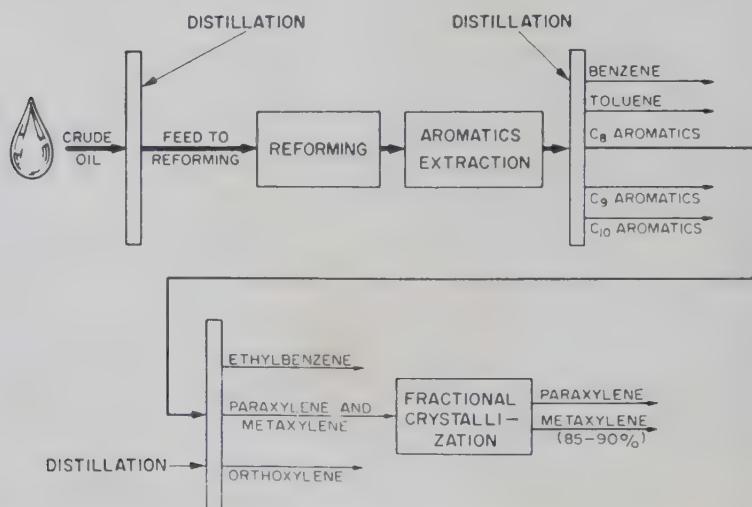


Fig. 14. Schematic diagram for production of aromatic hydrocarbons from petroleum.

catalytic reforming of virgin naphthas is shown in Tables 4 and 5. A catalytic reformer unit is shown in Fig. 13.

Fig. 14 shows a schematic flow diagram for the manufacture and recovery of aromatic hydrocarbons from petroleum.

p-Cymene (*p*-isopropyltoluene) is unusual in that it represents one of the few instances in which an aromatic hydrocarbon is obtained from a natural source other than coal or petroleum. It is a constituent of many essential oils and is obtained commercially from old stumps of the longleaf and slash pines (*Pinus palustris* and *Pinus caribaea*). The chief constituents of these oils are terpenes but small amounts of *p*-cymene are present. It can be obtained by the distillation of the fruit



Pine stumps enroute to shredder.

(Courtesy Hercules Powder Co., Inc., U.S.A.).

or seed of *Cumin cyminum*, a herb similar to caraway. Essential oils distilled from the flowering plants of thyme, chenopodium, monarda and origanum also contain *p*-cymene. Leaves of eucalyptus and cypress contain *p*-cymene which can be recovered by distillation.

The naval stores industry is the major producer of *p*-cymene. Turpentine and rosin are the primary products extracted from the old stumps of longleaf and slash pines by chemical processes and methods (Fig. 15). The volatile fraction is distilled to obtain the turpentine and large amounts of *p*-cymene are also obtained by this process. In the production of pulp from pine wood by the sulfite process of making paper, sulfite wood turpentine and *p*-cymene are important by-products.

USES OF AROMATIC HYDROCARBONS IN INDUSTRY

The principal uses of the aromatic hydrocarbons in industry are the following:

- (1) Starting materials and intermediates for synthesis of plastics, paints, pesticides, protective coatings, resins, dyes, drugs, flavors, perfumes and vitamins.
- (2) Solvents for paints, dyes, resins, inks, lacquers, rubbers and plastics.
- (3) Constituents of aviation and automotive gasoline.

For chemical synthesis a single aromatic hydrocarbon of high purity may be used whereas solvents may consist of a single hydrocarbon or a mixture of a number of hydrocarbons.

The aromatic hydrocarbons obtained from petroleum and their derivatives come under the definition of petrochemicals, chemicals derived from petroleum or natural gas. The petrochemical industry, which had its birth in 1919 in the Bayway refinery (Standard Oil of New Jersey), is one of the most rapidly growing phases of the oil industry.

The dramatic growth of the petrochemical industry seems to have developed from forces set in motion during World War

years toluene had been made as a by-product of the steel industry. By 1942, war requirements for explosives required a greater amount of this hydrocarbon for TNT. Petrochemicals supplied this increased demand so that during the war 83 percent of the total United States production of toluene came from petroleum. The war also supplied the impetus for the development of synthetic rubber as a result of dwindling imports of natural rubber. By 1945 the production of butadiene-styrene GR-S synthetic rubber reached 790,000 tons a year in the U.S.A. This was the first successful production of synthetic rubber from petroleum sources. The Germans had synthesized rubber in large quantities from butadiene and styrene derived from coal.

Post-war expansion has continued to supply the demand for aromatic petrochemicals for synthetic detergents, fibers, plastics and resins. In 1948, *o*-xylene became available from petroleum (Standard Oil of California) as a source of phthalic anhydride. At the time this is written, 1960, at least two American oil companies have decided to produce naphthalene commercially from petroleum and the polymethylbenzenes (mesitylene, pseudocumene, hemimellitene, durene, isodurene and terephthalene) may give rise to a new petrochemical boom.

Petroleum has been called many things by many people, such as 'black gold', 'life blood of industry', 'pillar of world economy', 'subterranean migratory embalming fluid'. It has in recent years become 'the chemist's Pandora's Box' to describe the growing trend to use oil as a source of new chemicals rather than a raw material separated by heat and distillation into a few fractions for fuels and lubricants.

A wide variety of chemical intermediates and end products from aromatic hydrocarbons is shown in Table 6.

TABLE 6

CHEMICAL INTERMEDIATES AND END PRODU

<i>Hydrocarbon</i>	<i>Intermediates</i>
Benzene	Ethylbenzene Chlorobenzene Benzene sulfonic acid Cyclohexane Nitrobenzene Dodecylbenzene Cumene Benzene hexachloride Maleic anhydride Anthraquinone Benzene <i>m</i> -sulfonic acid 1,2,4,5-Tetrachlorobenzene
Toluene	Trinitrotoluene Vinyl toluene Di-isocyanates
Xylenes	<i>o</i> -Xylene <i>p</i> -Xylene <i>m</i> -Xylene
Naphthalene	β -Naphthalene sulfonic acid Phthalic anhydride

ED FROM AROMATIC HYDROCARBONS*

<i>Intermediates</i>	<i>Products</i>
Styrene	Plastics
Phenol	Rubber
Aniline	Weed killers
p-Dichlorobenzene	DDT
m-Dichlorobenzene	Dyes
Phenol	Insecticide
Adipic acid	Solvent
Cyclohexanone	Resins
Aniline	Fibers
Dodecylbenzene sulfonate	Nylon
Phenol	Drugs
Acetone	Detergents
Maleic alkyd resins	Solvent
Maleic acid copolymers	Lindane
Resorcinol	Surface coatings
2,4,5-Trichlorophenol	Polyester resins
	Soil conditioners
	Dyes
	Adhesives
	Herbicide
	Solvent
	Explosives
	Surface coatings
	Adhesives
	Solvent
Phthalic anhydride	Alkyd resins
Isophthalic acid	Fibers
Phthalic acid	Plasticizers
Naphthol	Dyes
Alkyd resins	Surface coatings
Alkyl phthalates	Plasticizers
Anthraquinone	Dyes

TABLE 6 (continued)

<i>Hydrocarbon</i>	<i>Intermediates</i>
Anthracene	Anthraquinone
Indene	Coumarone-indene resins
Tetralin	
Pseudocumene	
	Durene
Diphenyl	
	Benzidine
Mesitylene	
Methylated naphthalenes	Naphthoic acids
Durene	Pyro-mellitic di-anhydride
<i>p-tert</i> -Butyltoluene	

* Compiled from Earhart, H. W. *et al.* (1959) and U. S. Steel (19

<i>Intermediates</i>	<i>Products</i>
	Dyes
	Asphalt tile
	Solvent
	Solvent
	Disinfectant
Pyro-mellitic di-anhydride	Pyro-mellitic acid
	Heat exchanger
	Disinfectant
	Fungicide
	Dyes
	Solvent
	Dyes
	Dyes
	Solvents
	Heat exchangers
Pyro-mellitic acid	Plasticizers curing agents
	Solvent drugs

Physical properties and methods of analysis for the aromatic hydrocarbons

PHYSICAL PROPERTIES

The liquid aromatic hydrocarbons are highly refractive, colorless substances, very sparingly soluble in water, having a low viscosity and low surface tension. Alkylation of the benzene ring diminishes the solubility in water. The water solubility of the mono-*n*-alkyl benzenes decreases with the length of the side chain as shown in Fig. 16. The boiling points show a regular

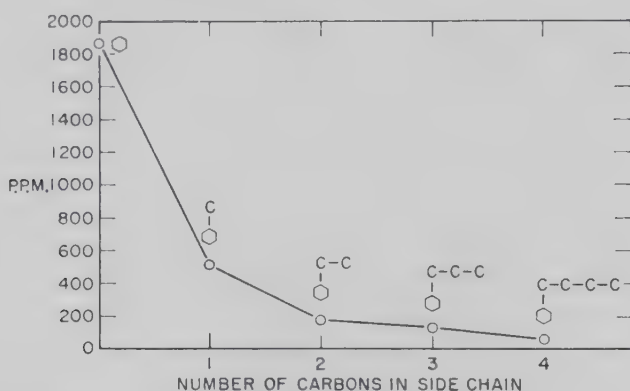


Fig. 16. Solubility of mono-*n*-alkylbenzenes in water.

(Gerarde, H. W., 1959)

relationship to the molecular weight and are almost independent of the position of the substituents in the ring. A similar progressive decrease in volatility with increasing molecular weight accompanies the lengthening of the alkyl chain. Symmetrical alky-

benzenes usually melt at higher temperatures than unsymmetrical isomers. The symmetrical 1,2,4,5-tetramethyl derivative, p-tetramethylbenzene, is a white solid at room temperature, whereas 1,2,3,5-tetramethylbenzene, isodurene, and 1,2,3,4-tetramethylbenzene, p-tetramethylbenzene, are liquids. Hexamethylbenzene, hexaethylbenzene, and *p*-di-*tert*-butylbenzene are white solids at room temperature.

TABLE 7

PHYSICAL PROPERTIES OF

PRINCIPAL CONDENSED AND NON-CONDENSED

POLYCYCLIC AROMATIC HYDROCARBONS USED IN INDUSTRY

<i>Name</i>	<i>Formula</i>	<i>M.P.</i>	<i>F.P.</i>
Diphenyl	$C_6H_5 \cdot C_6H_5$	70.5	254
Terphenyl	$C_6H_5 \cdot C_6H_4 \cdot C_6H_5$	171	—
Quaterphenyl	$C_6H_5 \cdot C_6H_4 \cdot C_6H_4 \cdot C_6H_5$	320	428
1,3,5-Triphenylbenzene	$1,3,5 (C_6H_5)_3 C_6H_3$	174.5	
Naphthalene	$C_{10}H_8$	80.2	217.9
1-Methylnaphthalene	$C_{10}H_7 \cdot CH_3$	—33	244.6
2-Methylnaphthalene	$C_{10}H_7 \cdot CH_3$	33.5-33.8	241.0
1,2-Dimethylnaphthalene	$C_{10}H_6 \cdot (CH_3)_2$	—8 to —11	271.7
1,4-Dimethylnaphthalene	$C_{10}H_6 \cdot (CH_3)_2$	82	269.1
1,5-Dimethylnaphthalene	$C_{10}H_6 \cdot (CH_3)_2$	—20	265.6
1,6-Dimethylnaphthalene	$C_{10}H_6 \cdot (CH_3)_2$	—16.5 and —35.0*	262.9
1,2,3-Dimethylnaphthalene	$C_{10}H_6 \cdot (CH_3)_2$	104-105	269.6
1,2,4-Dimethylnaphthalene	$C_{10}H_6 \cdot (CH_3)_2$	110-112	262.3
1,2,5-Dimethylnaphthalene	$C_{10}H_6 \cdot (CH_3)_2$	96-97	262.8
1,2,7-Trimethylnaphthalene	$C_{10}H_5 \cdot (CH_3)_3$	13.5	281.3
1,2,8-Trimethylnaphthalene	$C_{10}H_5 \cdot (CH_3)_3$	25.3	288.0
1,2,6-Trimethylnaphthalene	$C_{10}H_5 \cdot (CH_3)_3$	100-102	288.1
Anthracene	$C_{12}H_{10}$	94-95	278.2
Phenanthrene	$C_{14}H_{10}$	217	340.1
Fluorene	$C_{14}H_{10}$	99-100	336.5
Pyrene	$C_{16}H_{10}$	149-151	393.5

crystallizes in 2 modifications.

Diphenyl, the terphenyls, naphthalene and the polycyclic aromatic hydrocarbons are solids at room temperature. The alkyl naphthalenes may be liquids or solids at room temperature depending on the position, the length, and number of alkyl groups in the molecule.

Some physical properties of the condensed and non-condensed aromatic hydrocarbons and their alkyl derivatives are summarized in Table 7. Similar data on the alkylbenzenes, and methylnaphthalenes are shown in Tables 3, 4 and 5. Additional information on physical properties of specific hydrocarbons is given in Chapters 7 to 12.

The aromatic hydrocarbons absorb radiation in the ultraviolet and infrared portions of the spectrum, which forms the basis for the qualitative and quantitative analysis of these hydrocarbons in air and biological fluids.

ANALYTICAL PROCEDURES

The methods of analysis for the aromatic hydrocarbons depend on certain physical or chemical properties inherent in the hydrocarbon molecule. This forms the basis for grouping the methods into physical and chemical procedures. In many instances the actual analysis is a combination of both methods.

A. Physical methods

(1) *Combustion (Combustible gas or thermal indicators)*

A mixture of air and hydrocarbon vapor is oxidized or burned catalytically by passing the sample across a hot wire or filament. The burning results in a temperature increase in the hot filament which increases the resistance to the flow of electricity through the wire. The increase in resistance is directly proportional to the amount of combustible gas in the air sample. The instruments are calibrated for each combustible vapor. Readings are made directly by measuring the deflection of a needle across a calibrated scale.

Combustible gas or thermal indicators are portable instruments for field work used primarily for locating leaking gas and testing flammable gas hazards (Fig. 17). Although these instruments are intended to detect concentrations of combus-



17. Combustible gas indicator.

(Courtesy Davis Emergency Equipment Co., U.S.A.).

e vapors in the range of the lower explosive limit (10,000 p.p.m.), their sensitivity for aromatic hydrocarbons may be as low as 20 p.p.m.

Refractive index (The interferometer)

The index of refraction, a specific molecular property of chemicals, is used for the quantitative analysis of aromatic hydrocarbons in air or in liquid samples. In general, vapors of chemicals with a molecular weight of 100 or less can be determined

in concentrations below 100 p.p.m. The portable gas interferometer (Fig. 18) accurately measures minute changes in refractivity which makes it possible to determine low concentrations of gases or vapors in the atmosphere. Since refractivity is affected

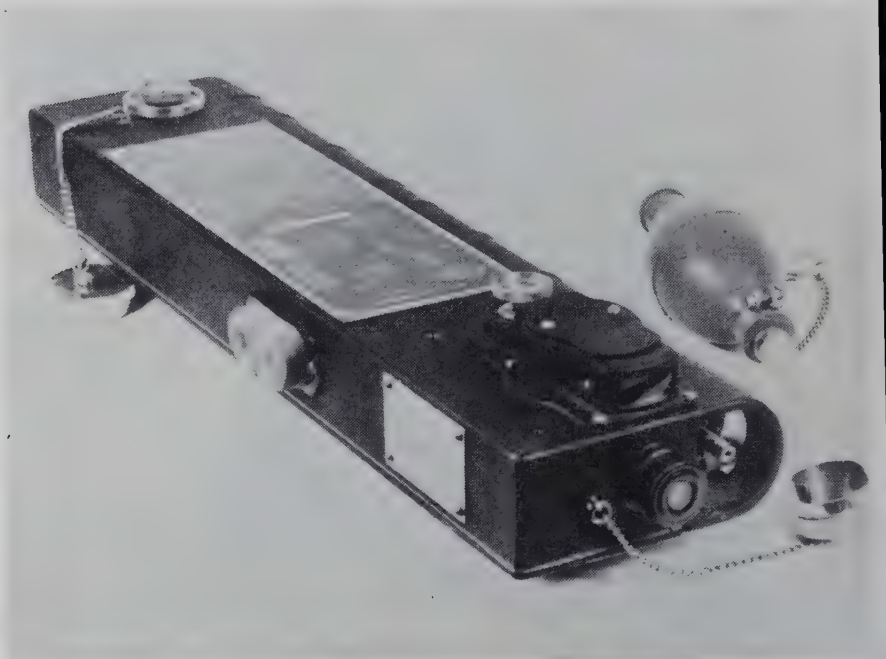


Fig. 18. Portable gas interferometer.

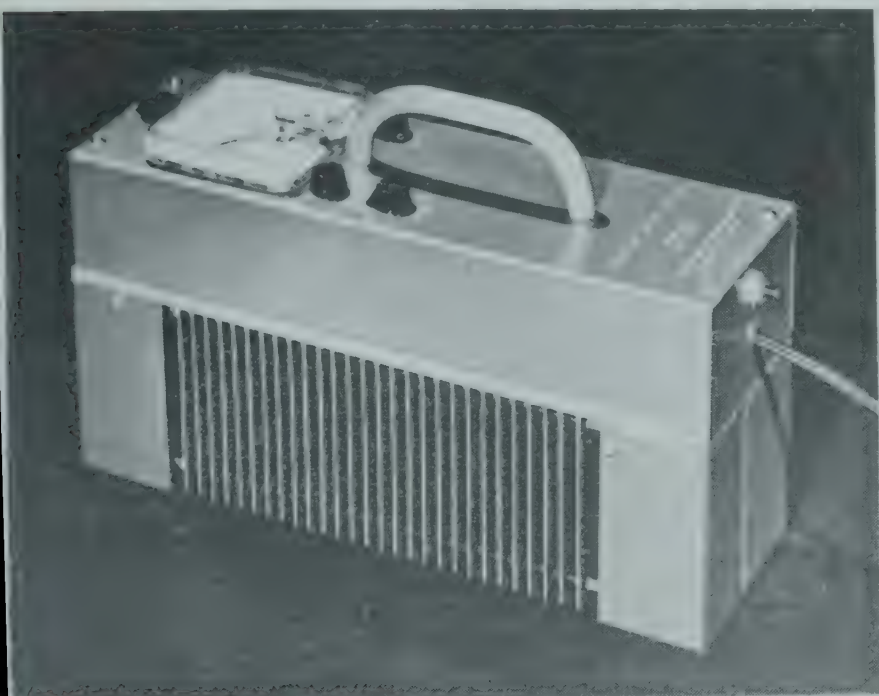
(Courtesy National Mine Service Company, Pittsburgh, Pa., U.S.A.)

by density of the gas, temperature and pressure must be controlled. For air analysis a dry air sample, free of carbon dioxide, is used as a standard for comparison with the gas sample to be measured. The interferometer is calibrated against known mixtures of vapor in air so that instrument scale readings can be converted to vapor percentages by reference to reliable data on the refractivity of gases and vapors. This is the reason for including the index of refraction in the physical properties of the aromatic hydrocarbons discussed in detail in this volume in Chapters 7 to 12.

The aromatic hydrocarbons in air can also be determined by measuring the index of refraction of the liquid condensate from an air sample.

Absorption of ultraviolet light

The absorption of ultraviolet light by the aromatic hydrocarbons has formed the basis for their qualitative and quantitative analysis in air and in biological samples (tissues, urine and blood). The absorption patterns of the aromatic hydrocarbons in the



19. *Portable ultraviolet photometer.*

(Courtesy Harold Kruger Instruments, San Gabriel, Calif., U.S.A.).

Ultraviolet region of the spectrum are useful for identification of small amounts of the hydrocarbons but maximal absorption at a specific wave length has been most useful for quantitative analysis.

The concentration of aromatic hydrocarbon vapors in air may

be determined with a direct-reading, portable ultraviolet photometer (Fig. 19). After standardizing the instrument against an internal standard for a specific aromatic hydrocarbon, it is ready to use for analysis of this hydrocarbon in the atmosphere.

The aromatic hydrocarbons may be collected from the

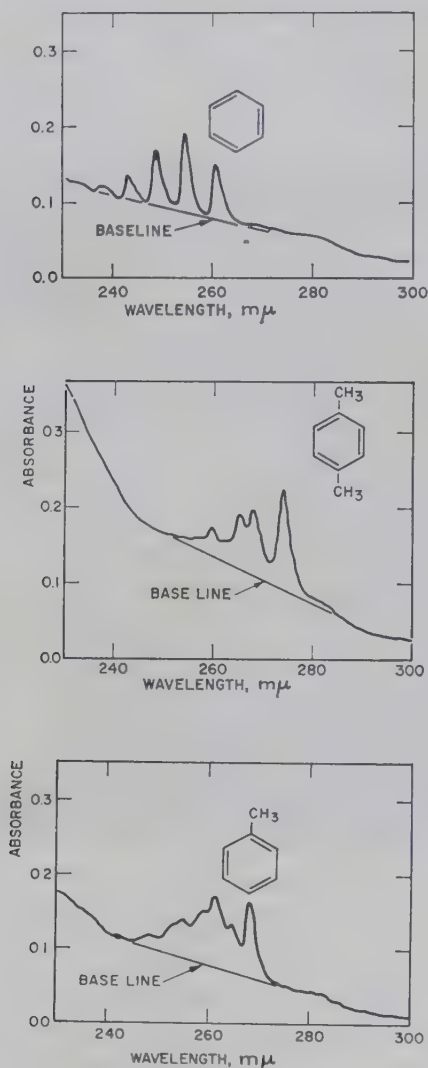


Fig. 20. Ultraviolet absorption of cyclohexane extracts of rat blood containing resp. a: 48 p.p.m. benzene, b: 26 p.p.m. p-xylene and c: 41 p.p.m. toluene.

(Guertin, D. L. and Gerarde, H. W., 1959)

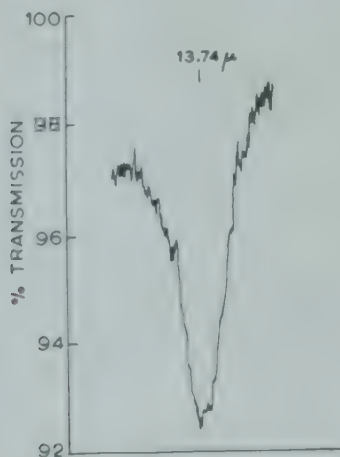
condensation, by absorption on silica gel or by scrubbing with a non-volatile solvent which does not have an interfering absorptive pattern (Övrum, P., 1956; Elkins, H. B., 1959).

In a study of the chemical contaminants in city air, the polycyclic aromatic hydrocarbons were determined spectrophotometrically after chromatographic separation on alumina (Wedgwood, P., and Cooper, R. L., 1956). A mixture of polycyclic aromatic hydrocarbons can be separated by paper chromatography and made visible by exposure to ultraviolet light (Bergmann, E. D. and Gruenwald, T., 1957).

For biological sample analysis the hydrocarbons can be extracted with cyclohexane or isooctane and the absorption of the extract determined with an ultraviolet spectrophotometer. Figure 20 shows the ultraviolet absorbance of benzene, toluene and xylene extracted with cyclohexane from blood taken from animals dosed with these hydrocarbons.

Absorption of infrared radiation

Infrared absorption has been used primarily for qualitative analysis and identification rather than quantitative measurement



1. Trace of the 13.74μ band of toluene with 86 micromicroliters (10^{14} molecules) in a demountable ultramicro cell. Solvent: methylhexane. Cell path: 0.02 mm. Cell area: 1 mm^2 .

(Courtesy Beckman Scientific Instruments Co. Inc., U.S.A.).

of aromatic hydrocarbons. Positive identification of single compounds can be made since each molecule has its characteristic infrared absorption pattern or 'molecular fingerprint'. With development of micro sampling accessories and techniques, micro quantities ($0.1 \mu\text{l}$ of liquid, $50 \mu\text{g}$ of solid, and 0.25 ml of gas) can be identified and analyzed. Fig. 21 shows an example of the sensitivity attainable with infrared analysis for the detection of toluene which has strong absorption at 13.74μ . The tracing was obtained from 86 micro-microliters of toluene (5×10^{14} molecules!) diluted with methylcyclohexane.

In recent years continuous non-dispersive infrared gas analyzers have become available for analysis of a single hydrocarbon or a complex mixture of gases or liquids. An important application of these instruments is in the measurement of toxic and combustible gases or vapors in the plant or in public health

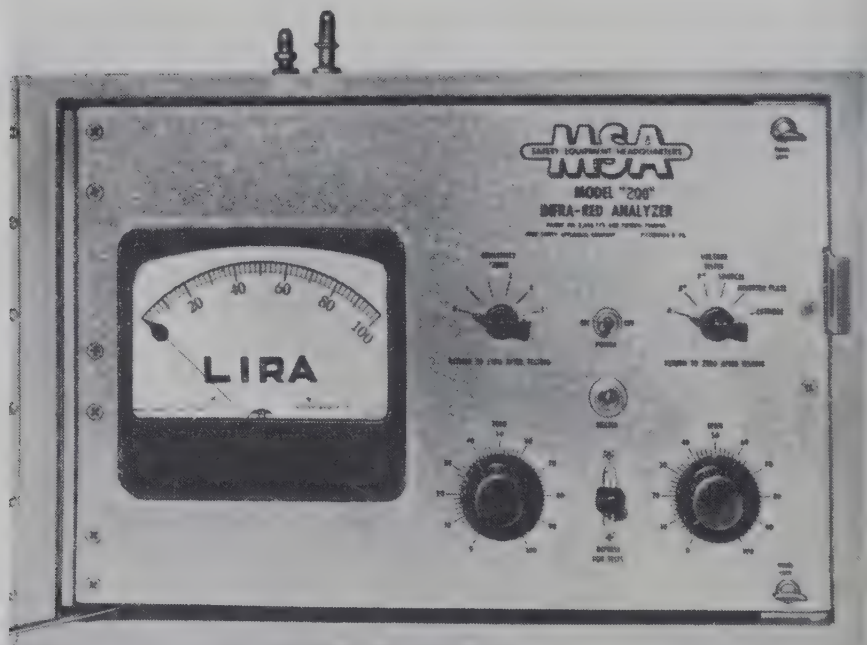


Fig. 22. Infrared analyzer.

(Courtesy Mine Safety Appliances Co. Inc., U.S.A.)

air pollution work. Continuous monitoring of hydrocarbons ranging from 0 to 3 p.p.m. is possible with the infrared analyzer (Fig. 22).

Polarography

Several different polarographic procedures were used by Eby (1953) for predicting tumor potency of high boiling petroleum fractions containing polycyclic aromatic hydrocarbons. The methods were based on the fact that the reduction potentials for the anthracene derivatives were lower than the reduction potentials of other aromatic hydrocarbons. The polarographic method appears to be comparable with other non-chemical methods, such as the Esso 'caffeine number' method (Fig. 37), in its precision for predicting tumor potency of high boiling petroleum fractions.

Chemical methods

Chemical procedures for the qualitative and quantitative analysis of aromatic hydrocarbons in air and biological materials are based on the production of colored compounds by oxidation, diarylmethane dye formation, or molecular complexing.

The deposition of the color-forming chemicals on the surface of silica-gel granules sealed in glass detector tubes has greatly simplified the quantitative analysis of monocyclic aromatic hydrocarbons in air (benzene, toluene, xylene). The sealed ends of the detector tube are broken off and a measured volume of air is drawn through the tube. The concentration of the hydrocarbons is proportional to the length of the colored stain in the tube (Fig. 23). The test is non-specific since the color depends on the presence of the benzene ring in the aromatic hydrocarbon.

The concentration of monocyclic aromatic hydrocarbons in air can also be determined by bubbling air directly into a potassium dichromate mixture or sulfuric acid-formaldehyde mixture and

measuring the color intensity against a standard, or with a colorimeter (U. K. Leaflet No. 4, 1950; Truffert, L., 1952).

The quantitative analysis of aromatic hydrocarbons in biological fluids (urine and blood) and tissues requires a preliminary

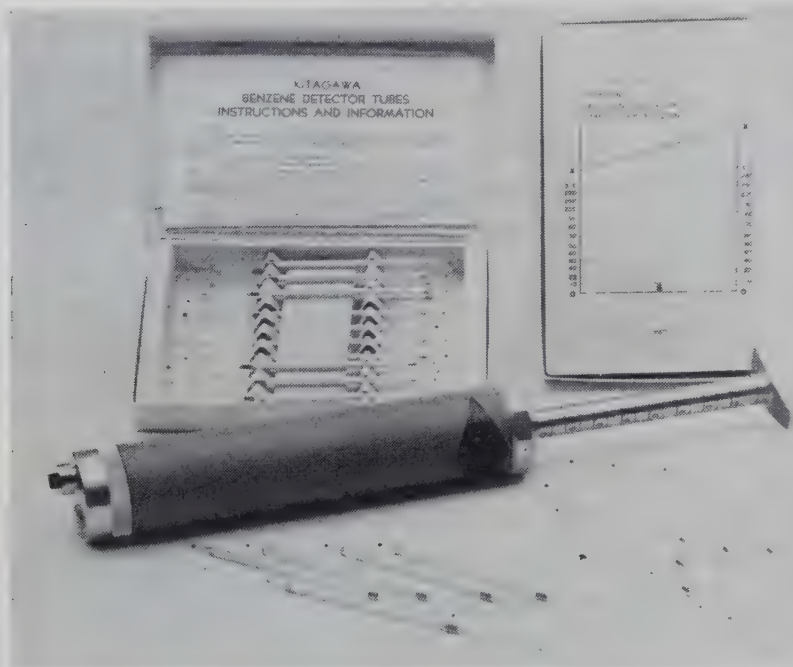


Fig. 23. Kitagawa gas detector-Unico model No. 400.

(Courtesy Union Industrial Equipment Co., Port Chester, N.Y., U.S.)

separation of the hydrocarbon from the sample by extraction with a solvent or by distillation. The aromatic hydrocarbon is subsequently nitrated or reacted with a sulfuric acid-formaldehyde mixture to form colored compounds which are measured colorimetrically (Yant, W. P. *et al.*, 1935).

Sensitive color tests have recently been described for the qualitative and quantitative analysis of polynuclear aromatic hydrocarbons. Brilliantly colored diarylmethane dyes are formed by the reaction of the hydrocarbon with benzal or piperonal in the presence of phosphorus pentachloride in trifluoroacetic acid (Sawicki, E. *et al.*, 1958). Color complexes are formed by the interaction of polynuclear aromatic hydrocarbons with certain dyes.

hydrocarbons with 2,4,7-trinitrofluorenone (Gordon, T. and Hureau, M. J., 1959). Some of the complexes also show brilliant ultraviolet fluorescence. Qualitative information about the structure of unknown compounds can be derived by observing the color and fluorescence of the trinitrofluorenone complex on a paper chromatogram and by determining the solubility of the complex in isooctane and ethyl alcohol.

A mixture of polynuclear hydrocarbons can be separated by paper chromatography and the individual spots made visible by spraying with a 20% solution of antimony pentachloride or carbon tetrachloride (Bergmann, E. D. and Gruenwald, T., 1959).

Physical-chemical methods

Many analytical procedures for the analysis of aromatic hydrocarbons are combinations of the chemical and physical methods described above. Chemical separation of aromatic hydrocarbons by solvent extraction, silica gel absorption, and elution or distillation may be combined with ultraviolet, infrared or colorimetric procedures. The combination procedures are used particularly for analysis of aromatic hydrocarbons in biological materials.

The Esso 'caffeine number' method is a physical-chemical procedure for predicting the carcinogenic potency of certain boiling petroleum products (Eby, L. T. *et al.*, 1953). The caffeine number is the difference in the absorbances at 340 and 360 $m\mu$ of an aqueous caffeine extract of a solution of 2.00 g of sample in 10.0 ml of *n*-heptane and 10.0 ml of toluene. The solution employed in the reference cell of the spectrophotometer is the 0.1 *M* caffeine solution used for the extraction.

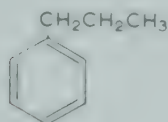
Toxicological effects of the aromatic hydrocarbons

EFFECTS ON THE CHEMICAL SENSES

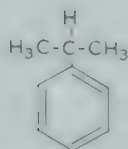
A. Odor

The expression 'aromatic' hydrocarbon is historical, but is no longer justified by facts since compounds of unpleasant as well as agreeable odor are found in the class of hydrocarbons containing the benzene nucleus. In general, benzene and its more volatile homologues are characterized by a strong and rather pleasant odor. Adrian (1953) includes the aromatic hydrocarbons as one of the four principal groups of olfactory stimulants. The other three groups are the paraffin hydrocarbons, the terpenes, and the ethers, esters and ketones.

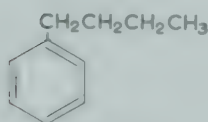
The quality and intensity of the odor of the alkyl derivatives of benzene depend on the number of alkyl groups and the length, degree of saturation and branching of the side chains in the hydrocarbon molecule. In general, lengthening of the side chain diminishes the perceptible odor of the compound since the vapor pressure decreases with increasing molecular weight. Phenyl dodecane, for example, is practically odorless and the same is true of the aromatic hydrocarbons, durene, *p*-di-*tert*-butylbenzene, hexamethylbenzene and hexaethylbenzene, are devoid of odor. Branching and unsaturation of the chain enhance the odor of the corresponding straight-chain isomer, which is bland and fatty in comparison with the sharp, intense quality of the branched-chain isomer. The changes in odor associated with branching are



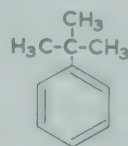
n-Propylbenzene
(Sweet, bland)



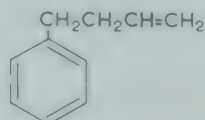
Isopropylbenzene
(Sharp, penetrating)



n-Butylbenzene
(Sweet, bland)

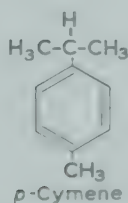


tert-Butylbenzene
(Sharp, penetrating)

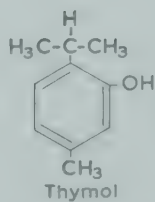


4-Phenylbutene-1
(Sharp, penetrating)

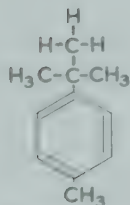
24. Influence of branching and unsaturation of the side chain on the
of propyl- and butylbenzenes. (Gerarde, H. W., 1959).



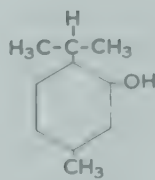
p-Cymene



Thymol



p-*tert*-Butyltoluene



Menthol

Multiple methylation on single carbon enhances odor.
(Gerarde, H. W., 1959).

unsaturation of the side-chain are illustrated by the isomers propyl- and butyl-benzene shown in Fig. 24. Multiple methylation on a single carbon atom is associated with the odor of menthol and similar compounds shown in Fig. 25. The propyl group is present in cumene and cymene. *p*-Cymene is a constituent of eucalyptus oil, which has been used for centuries to relieve nasal congestion. Odor is associated with a tendency to cause mucous membrane irritation. This will be discussed further in the section describing the local effects of the aromatic derivatives of benzene on mucous membranes and skin.

The term 'olfactory' has been suggested to denote the number of molecules per cubic centimeter of air which can just be detected. The value for benzene is 4×10^{11} , which is equal to about 5×10^{-11} grams!

The olfactory 'threshold limits' for some aromatic hydrocarbons are shown in Table 8. Cyclohexane is included for comparison.

TABLE 8
ODOR 'THRESHOLDS' FOR ALKYL DERIVATIVES OF BENZENE
(Cyclohexane shown for comparison)

Hydrocarbon	Vapor concentration (p.p.b.)
Benzene	1500
<i>p</i> -tert-Butyltoluene	5000 ^a
<i>alpha</i> -Methylstyrene	> 10,000 ^b
Styrene	8.5-44.5 ^c
Styrene	> 10,000 ^b
Toluene	480
Vinyltoluene	> 10,000 ^b
<i>o</i> -Xylene	170
Cyclohexane	300,000

^a Hine, C. H. *et al.* (1954).

^b Wolf, M. A. *et al.* (1956).

^c The air over Louisville (1958).

son. Note the great difference in the olfactory threshold between the aromatic hydrocarbons and the saturated analogue of benzene.

The minimum olfactory perception threshold varies greatly in individuals. Nader (1958) found that the individual perception thresholds (IPT) for toluene ranged from 21 to 510 parts per billion in four subjects tested.

The sense of smell is probably man's finest analytical sensory apparatus. It can be developed to detect and identify an unlimited range of chemicals and specific parts of molecules. The benzene ring in the volatile aromatic hydrocarbons is one of the most powerful osmophoric molecular moieties. The odor of naphthalene is probably the most familiar of the hydrocarbon odors because of its extensive use as 'moth balls'. Alkyl naphthalenes have a similar odor. With a little training of the olfactory bulb, one can readily learn to detect other aromatic hydrocarbons by their characteristic odors. As with other sensory chemicals, olfactory sensitivity to the aromatic hydrocarbons diminishes with prolonged exposure due to olfactory fatigue.

Taste

Liquid aromatic hydrocarbons have powerful effects on the gustatory receptors. Benzene and the liquid alkylbenzenes with short chain alkyl groups (methyl, ethyl, propyl) produce a sharp, tingling sensation on contact with the taste buds. This is followed by a feeling of numbness or loss of sensation due to local anesthesia. Branching of the side chain intensifies the effect. Isopropylbenzene (cumene) produces a warm, burning, painful sensation on contact with the tongue causing excessive salivation. After the cumene is washed out of the mouth with water, a lingering residual sweet taste remains. It is certainly understandable why benzene, which was used to treat malaria a few years ago, was administered in a gelatin capsule. A cubic centimeter of 1,2-diethylbenzene diluted in a pint

of cold chocolate malted milk (about 1 to 500 dilution) causing tingling, numbness and anesthesia of the mucous membrane of the mouth and throat. The diethylbenzene, diluted and covered by the ice cream, still imparts a powerful odor and taste of camphor to the drink.

As the length of the alkyl group increases, the taste of alkyl derivatives of benzene becomes more bland and oily. In a figurative mathematical sense the taste is 'asymptotic' to that of the corresponding aliphatic hydrocarbon. Phenyl dodecane is bland and oily in taste. Detergent alkylate, 'dodecylbenzene' (a commercial mixture of branched C_{12} alkylbenzenes) is less bland than phenyldodecane probably because of multiple branching of the side chain. The solid alkylbenzenes are insipid, do not produce any sensation on contact with taste buds, and do not cause local anesthesia.

Naphthalene has a 'camphor-like' taste which some individuals find pleasurable. Harries and Hughes (1958) reported that naphthalene 'moth balls' were one of the favorite dietary items in a list of substances often craved by pregnant women. A case of chronic naphthalene intoxication was reported in an office worker who had a craving for 'moth balls'. They were kept in the desk drawer and eaten like candy during the day! (Klorer et al., 1953).

Naphthalene undoubtedly contributed to the 'bouquet' of the 'moth ball' cocktail which was responsible for 50 cases of severe intoxication due to ingestion of a drink called 'scrap-iron' (Gadsden, R. *et al.*, 1958). This beverage, which has been described as a drink of 'voltage rather than vintage', consisted of naphthalene dissolved in isopropyl alcohol contained in a galvanized metal can.

EFFECTS ON MUCOUS MEMBRANES AND SUBCUTANEOUS TISSUE

Benzene and the liquid alkyl derivatives of benzene on contact

the mucous membranes cause local irritation and vasodilation. This property diminishes in potency with the lengthening of the alkyl substituent and multiplicity of the alkyl groups. Branching and unsaturation of the chain tend to increase the local irritation potency.

Direct contact of the liquid aromatic hydrocarbons with pulmonary tissue causes chemical pneumonitis characterized by pulmonary edema, hemorrhage, and tissue necrosis. The aspiration of a small volume of liquid hydrocarbon into the lungs can cause extensive pulmonary injury. This is presumably due to the low surface tension which allows the chemical to spread over a large surface. Fig. 26 shows the diffuse lung hemorrhage



Fig. 26. Gross appearance of rat heart and lungs after aspiration of 0.2 ml of xylene (Right and left; center, normal) (Gerarde, H. W., 1959).



Microscopic appearance of rat lungs after aspiration of 0.2 ml of xylene (Normal on right). Magnification $\times 430$. (Gerarde, H. W., 1959a).

produced in rats 10–15 minutes after the aspiration of 0.2 ml of kerosine. The microscopic appearance of the lung is shown in Fig. 27. These pulmonary changes are also produced by aspiration of liquid alkylbenzenes, alkyl naphthalenes, indanones, indenes and commercial hydrocarbon mixtures containing these hydrocarbons (Gerarde, H. W., 1959).

The subcutaneous injection of the liquid aromatic hydrocarbons produces an inflammatory reaction. The inflammatory response tends to diminish with the length and number of alkyl groups in the alkylbenzene group. The inflammatory reaction results in encystment and localization of the inoculum following subcutaneous injection in laboratory animals.

EFFECTS ON THE EYE

The direct contact of liquid or solid aromatic hydrocarbons with the eye causes itching, lacrimation and irritation. If contact is sufficiently prolonged, tissue injury may result. Conjunctival and corneal burns have been reported resulting from contact with ethylbenzene, styrene, toluene, benzene, tetralin, hexaethylbenzene and xylene (Toxic Eye Hazards, 1949). Opacity of the lens has been reported in workers exposed to naphthalene vapors (Ghetti, G., and Mariani, L., 1956). Naphthalene is one of a small number of substances which have been shown to cause cataracts in experimental animals (see Chapter 11). Lesions of the eyelids have been reported in individuals exposed to crude anthracene oils (Occupation and Health, 1930). Repeated exposure to high concentrations of solvent vapors (toluene) has caused corneal injury called 'Polisher's Keratitis' (see Chapter 1, page 146).

EFFECTS ON THE SKIN

Direct contact of benzene and the liquid alkyl derivatives with the skin causes vasodilatation, erythema and irritation.

on. This property is particularly potent in the xylenes which are used as rubefacients in the laboratory to increase blood flow in rabbit ears and rat tails. This effect decreases in intensity with the length of the side chain and with multiplicity of alkylation. Branching tends to increase the potency for local irritation. Toluene, phenyl, naphthalene and the alkyl naphthalenes are less irritating to the skin than the alkyl derivatives of benzene. Because of their low primary skin irritation potency, the mono-methyl naphthalenes (*alpha* and *beta*) have been extensively used as solvents for pesticides, such as DDT, which are expected to come in contact with skin in normal use. The less-refined petroleum fractions containing the methylated naphthalenes are contaminated with a skin-photosensitizing substance which has an absorption spectrum with a peak in the region of 3300–3400 Å. Prolonged or repeated skin contact with the liquid aromatic hydrocarbons will remove the natural cutaneous fats; this may cause drying, scaling, and fissuring of the skin. This is a non-specific effect which may result from repeated skin contact with a liquid fat solvent.

In general, the aromatic hydrocarbons are absorbed slowly through the intact skin. The occurrence of systemic intoxication from skin contact with the aromatic hydrocarbons is highly improbable. The aromatic hydrocarbons are probably absorbed through the skin transfollicularly since this is the route of absorption of lipid soluble molecules. There is insufficient information to correlate the chemical constitution of the alkylbenzenes with skin penetration potency. The limited studies reported by Lalette and Cavier (1954) suggest that branching of the side chain tends to increase the rate of percutaneous penetration as shown in Fig. 28.

Repeated, prolonged exposure to the hydrocarbons present in crude oils, coal tar and pitch, creosote and petroleum 'slack' (i.e., unpurified) have caused cutaneous cancers in workers. The carcinogens in these complicated mixtures of hydrocarbons are believed to be polynuclear hydrocarbons, some of

which have been isolated from these sources and have been shown to produce skin tumors in experimental animals. The subject of carcinogenesis due to the polycyclic aromatic hydrocarbons is discussed further in Chapter 12.

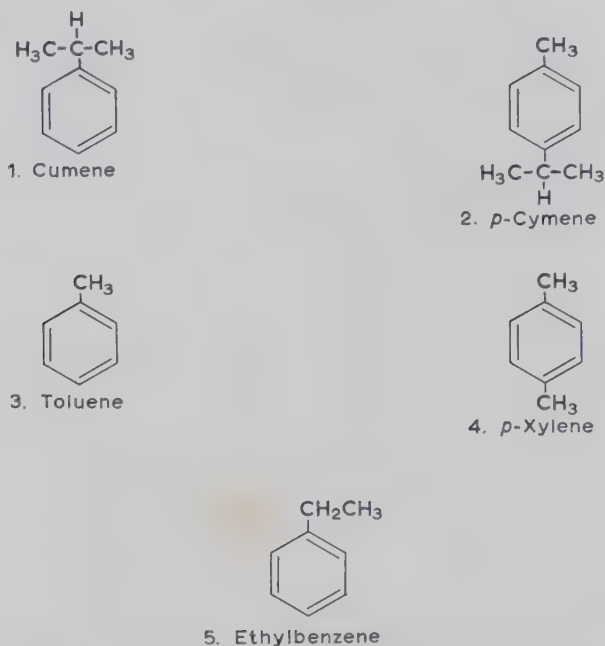


Fig. 28. Percutaneous penetration potency of some alkyl derivatives of benzene arranged in order of decreasing activity.

(Valette, G. and Cavier, R., 1954; Gerarde, H. W., 1954)

SYSTEMIC INTOXICATION

A. Acute toxicity

After absorption into the blood the aromatic hydrocarbons are in intimate contact with the endothelial cells of the blood vessels and capillaries. Local irritation of endothelial cells by the hydrocarbons may result in permeability changes in the capillaries. This leads to increased diapedesis, edema in surrounding tissue, petechial and gross hemorrhage. These changes are commonly seen in the lungs of animals dosed with alkylbenzenes intravenously.

trically, subcutaneously, or intraperitoneally. The degree of injury depends on the concentration of the hydrocarbon in the blood and the irritation potency of the hydrocarbon. The branched and unsaturated chain alkylbenzenes are more irritating than the corresponding unbranched and saturated alkylbenzene isomers. Although more than 40% of a single dose of benzene given intragastrically is eliminated through the lungs, gross pulmonary hemorrhage is seldom seen in benzene-dosed animals. The lungs appear hyperemic but gross pulmonary edema and hemorrhage are usually absent. Hyperemia and hemorrhage secondary to endothelial injury have been observed in the kidney, liver, spleen, bladder, thymus, brain and spinal cord after dosing with some of the alkyl derivatives of benzene (Gerarde, H. W., 1959).

The principal positive pathological findings in animals dosed with a large number of alkyl derivatives of benzene indicate that the injury is primarily of endothelial origin (Table 18, p. 62). Generalized hyperemia and hemorrhage of the lungs, thymus, spleen and gastrointestinal tract have also been observed in animals dosed orally with 1- and 2- mono-methyl and mono-ethyl alkylbenzenes (Gerarde, H. W., unpublished data).

The aromatic hydrocarbons have a particular affinity for nerve tissue because of its high lipid content. The presence of these hydrocarbons in the cells of the brain interferes with normal metabolic processes, resulting usually in signs and symptoms of central nervous system depression: sluggishness, stupor, anesthesia, narcosis and coma. This is in sharp contrast with strychnine, which is a neuroconvulsant producing stimulation characterized by tremors and convulsions. Convulsions and tremors commonly seen in animals dosed with benzene occur frequently in animals dosed with the alkyl derivatives of benzene.

The depressant action of the alkylbenzenes is similar to the action of alcohols, ketones, ethers, and esters, an effect which is structurally non-specific. The quality and intensity of the

effect is believed to depend on the number of molecules present at a particular moment in the cell, rather than the type of molecule. This concept of 'physical toxicity' is comparable to the *colligative property* described by the physical chemist. T

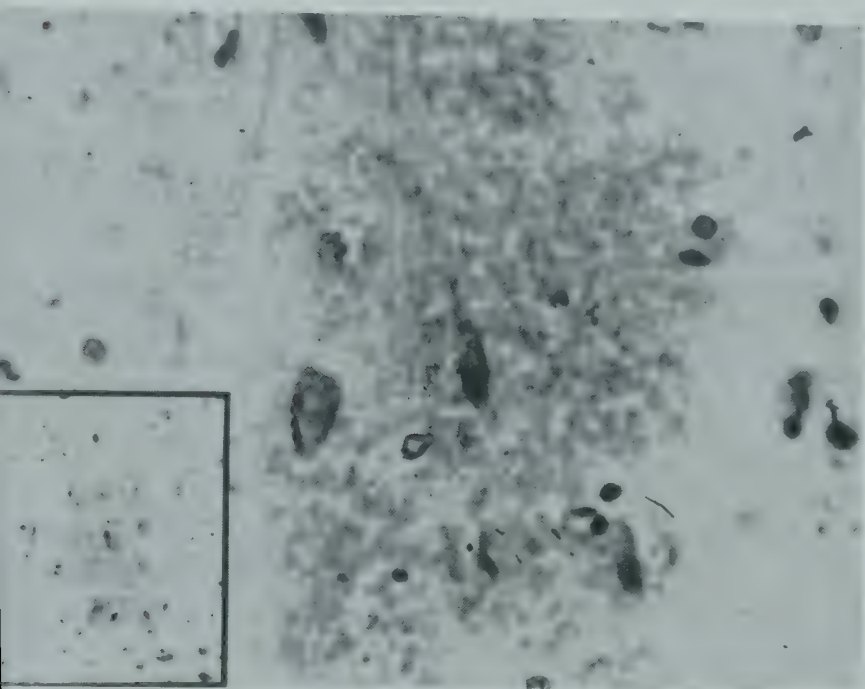


Fig. 29. Rat showing paralysis and contractures of front legs after a single oral dose of *p*-tert-butyltoluene. (Gerarde, H. W., 1955)

effect of solute on the vapor pressure, boiling point, and freezing point of a solution depends only on the number rather than the kind of molecules or ions dissolved in the solvent.

The narcotic potency of the alkylbenzenes depends on chain length, branching, and the number of alkyl groups attached to the benzene ring. The narcotic potency decreases marked

chain length, falling off at four carbon atoms and diminishing steadily, so that phenyldodecane has the narcotic potency (impotency) of mineral oil. Toluene and ethylbenzene are 'not-acting' by comparison with *n*-propyl and *n*-butylbenzene



30. Microscopic hemorrhage in spinal cord of rat after a single oral dose of *tert*-butyltoluene. Magnification $\times 430$, inset $\times 100$.

(Gerarde, H. W., 1959).

are slow in initiating the depressant effect on the central nervous system. The rate of action depends on the rate of absorption into the blood and transport to the brain. The rate of absorption into the blood stream depends on the water solubility of the hydrocarbon. Since the water solubility diminishes rapidly with chain length and multiplicity of alkylation, the absorption rate decreases with these changes in chemical constitution.

The duration of the central nervous system depressant effect of the alkylbenzenes increases with length and branching

of the side chain. Cumene and *n*-butylbenzene are 'long-acting' as compared with toluene and ethylbenzene which are 'short-acting'.

The prolongation of action accompanying branching and lengthening of the side chain is probably related to the rate of removal of the hydrocarbon from the cells in which they concentrate. This is dependent on the rate of biotransformation *in situ* and in other tissues (liver, kidney) into water-soluble metabolites. It appears that a branched side chain is oxidized more slowly than a straight chain having the same number of carbon atoms.

The depressant effect on the central nervous system lasts as long as the hydrocarbons are present in the nerve cells. Normal metabolic activity and full function usually return after the hydrocarbons are eliminated. This is characteristic of the physical toxicants. An overwhelming dose of a physical toxicant which produces profound narcosis, coma of long duration, and endothelial injury may result in permanent injury to the tissues of the central nervous system, particularly the brain. The injury is due to the lack of oxygenation of the brain cells during the interval of deep narcosis and hemorrhage due to endothelial

TABLE 9

Toxicity		LD-50	
Rating	Class definition	Rats-oral mg/kg	Rabbits-skin mg/kg
1	Extremely toxic	1 or less	5 or less
2	Highly toxic	1-50	5-43
3	Moderately toxic	50-500	44-340
4	Slightly toxic	500-5,000	350-2,810
5	Practically non-toxic	5,000-15,000	2,820-22,590
6	Relatively harmless	15,000 or more	22,600 or more

* After Hodge, H. C. and Sterner, J. H. (1943).

It is well established that oxygen deprivation of cerebral tissue may cause permanent injury.

The foregoing applies also to the alkyl derivatives of naphthalene. A single dose of 1- and 2- mono-methyl and mono-naphthalene (5 ml/kg by stomach tube) causes sedation, diminished rate of respiration and prolonged coma in the rat (Parde, H. W., unpublished data).

The neurotoxicity of *p*-*tert*-butyltoluene is believed to be a consequence of hemorrhage in the spinal cord due to vascular injury. The isopropyl, *sec*-butyl, and *tert*-butyl groups are more irritating than the corresponding straight-chain alkyl groups. Hemorrhage in the brain and spinal cord may lead to permanent injury. Fig. 29 shows a rat that suffered a permanent paralysis of the forelegs following the oral administration of a single dose of 0.75 ml of *p*-*tert*-butyltoluene in an equal volume of oil. The paralysis was secondary to hemorrhage in the white matter of the cervical and thoracic spinal cord (Fig. 30). The animal did not recover use of the forelegs, which ultimately became permanently contractured to the chest as shown in Fig. 29. Except for this deformity, it was normal in all respects.

ACUTE ORAL, CUTANEOUS AND INHALATION TOXICITY

LC-50 (approx.)

*Rats-inhalation 4 h
Mortality (2/6-4/6)*

*Probable lethal
oral dose
for Man*

< 10 p.p.m.	A taste; 1 grain
10-100 p.p.m.	1 teaspoon; 4 ml
100-1,000 p.p.m.	1 ounce; 30 g
1,000-10,000 p.p.m.	1 pint; 250 g
10,000-100,000 p.p.m.	1 quart
> 100,000 p.p.m.	> 1 quart

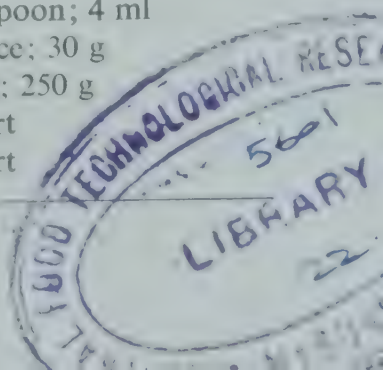


TABLE 10

ACUTE INHALATION TOXICITY

<i>Hydrocarbon</i>	<i>Animal</i>
Benzene ⁷	Rat
<i>p</i> - <i>tert</i> -Butyltoluene ⁶	Rat
Cumene ⁵	Rat
Diphenyl ⁴	Rat
Ethylbenzene ¹	Mouse
Propylbenzene ¹	Mouse
Styrene ³	Rat
Toluene ²	Mouse
<i>o</i> -Xylene ¹	Mouse
<i>m</i> -Xylene ¹	Mouse
<i>p</i> -Xylene ¹	Mouse

¹ Lazarew, N. V. (1929).³ Spencer, H. C. *et al.* (1942).² Svirbely, J. L. *et al.* (1943).⁴ Deichmann, W. B. *et al.* (1947).

TABLE 11

RELATIVE ACUTE VAPOR TOXICITY

<i>Hydrocarbon</i>	<i>B.P. (°C)</i>
Benzene	79.6
Toluene	110.5
Ethylbenzene	136.5
<i>o</i> -Xylene	144.0
<i>m</i> -Xylene	139.0
<i>p</i> -Xylene	137.7
<i>n</i> -Propylbenzene	157.5
Isopropylbenzene (Cumene)	153.4
<i>p</i> -Methylethylbenzene	162
1,2,4-Trimethylbenzene (Pseudo-cumene)	169.8
1,3,5-Trimethylbenzene (Mesitylene)	164.6
<i>n</i> -Butylbenzene	180.0
<i>p</i> -Diethylbenzene	183.0
<i>p</i> -Methylpropylbenzene	179.5-180.0

* After Lehmann, K. B. and Flury, F. (1943).

ROMATIC HYDROCARBONS

mg/l	Concentration		Duration of exposure (h)	Mortality (Per cent)
		p.p.m.		
51		16,000	4	50
1.5 ± .22		248 ± 36	4	50
39		8,000	4	50
0.3		—	7	0
45		10,382	2	100
20		4,100	2	100
23.2		5,000	8	100
19.9		5,300	7	50
30		6,920	2	100
50		11,540	2	100
15-35		3460-8075	2	100

yth, H. F. *et al.* (1951).

⁷ Carpenter, C. P. *et al.* (1949).

ne, C. H. *et al.* (1954).

L. DERIVATIVES OF BENZENE (MOUSE)*

Minimum concentration of vapors to cause					
Prostration		Loss of reflexes		Death	
l	p.p.m.	mg/l	p.p.m.	mg/l	p.p.m.
5	9,500	—	—	45	13,600
12	2,600-3,200	—	—	30-45	9,300-12,000
5	3,500	—	—	45	10,400
20	3,500-4,600	—	—	30	6,900
15	2,300-3,500	15?	3,500	50	11,500
0	2,300	—	—	15-35	3,100-7,100
15	2,000-3,100	15	3,100	20	4,100
0	4,100	25	5,100	—	—
5	3,100	—	—	—	—
0	8,200	40-45?	8,200-9,200	—	—
15	5,100-7,100	35-45?	7,100-9,200	—	—
5	2,700	—	—	—	—
0	5,500	—	—	—	—
0	9,100	—	—	—	—

TABLE 12
ACUTE ORAL TOXICITY OF AROMATIC HYDROCARBONS
(Albino rat)

<i>Hydrocarbon</i>	<i>Approximate LD50-mg/kg</i>
Benzene ¹	5,600
<i>p</i> - <i>tert</i> -Butyltoluene ⁴	1,600
Diethylbenzenes (25 % <i>o</i> -, 40 % <i>m</i> -, 35 % <i>p</i> -) ¹	1,200
Diphenyl (Biphenyl) ²	3,280
Ethylbenzene ¹	3,500
Isopropylbenzene (Cumene) ¹	1,400
<i>alpha</i> -Methylstyrene ¹	4,900
Naphthalene ⁵	> 1,000
Styrene ¹	5,000
Tetrahydronaphthalene (Tetralin) ³	2,860
Toluene ¹	7,000
Vinyltoluenes (55-70 % <i>m</i> -, 30-45 % <i>p</i> -) ¹	4,000
Xylenes (19 % <i>o</i> -, 52 % <i>m</i> -, 24 % <i>p</i> -) ¹	4,300

¹ Wolf, M. A. *et al.* (1956).

² Deichmann, W. B. *et al.* (1947).

³ Smyth, H. F. *et al.* (1951).

⁴ Hine, C. H. *et al.* (1954).

⁵ Chang, L. H. (1943).

Using the LD-50 and LC-50 as indices of acute toxicity, aromatic hydrocarbons, in general, can be classified as moderately toxic by inhalation and moderately to slightly toxic by the oral and percutaneous route of administration according to Table 9.

The acute toxicity of aromatic hydrocarbon vapors, mists, and dusts is summarized in Tables 10 and 11.

The acute toxicity of the aromatic hydrocarbons by the dermal route of administration is summarized in Tables 12 and 13. Detailed discussions of the toxicology of specific hydrocarbons are presented in Chapters 7 to 11.

TABLE 13

TOXICITY OF BICYCLIC (AROMATIC AND AROMATIC-ALICYCLIC)
HYDROCARBONS*

(Male Albino rats, single dose 5 ml/kg**)

<i>Hydrocarbon</i>	<i>Mortality in 10 dosed</i>
Amylbiphenyl	9
Benzylcyclohexane	2
1,6-Dimethylnaphthalene	7
Diphenylmethane	10
1-Ethylnaphthalene	10
2-Ethylnaphthalene	7
Indane (Hydrindene)	7
Indene	10
4-Isopropylbiphenyl	0
1-Methylnaphthalene	10
2-Methylnaphthalene	10
Phenylcyclohexane	3
Phenylcyclohexene	4

J.A. Arch. Ind. Health, Gerarde, H. W. (April 1959) and unpublished
hydrocarbon dissolved in an equal volume of olive oil.

as not been possible to collect sufficient quantitative data
e percutaneous toxicity of the aromatic hydrocarbons to
re a table of percutaneous LD-50's comparable with the
oral and acute inhalation toxicity tables. From the limited
available it appears that the most toxic aromatic hydro-
as belong in the moderately toxic class according to the
cation of percutaneous toxicants.

**e relationship between chemical constitution and toxicity of
alkyl derivatives of benzene**

romatic study of the toxicity of a relatively large number
lbenzenes has made it possible to draw certain conclu-

TABLE 14
 ORAL TOXICITY OF MONO-SUBSTITUTED ALIPHATIC
 DERIVATIVES OF BENZENE*
 (Male Albino rats, single dose 5 ml/kg**)

<i>Hydrocarbon</i>	<i>Mortality in 10 dosed</i>
Allylbenzene	8
<i>n</i> -Amylbenzene	0
<i>sec</i> -Amylbenzene	9
<i>tert</i> -Amylbenzene	5
Benzene	0
<i>n</i> -Butylbenzene	2
<i>sec</i> -Butylbenzene	8
<i>tert</i> -Butylbenzene	7
1-Dodecylbenzene (1-Phenyldodecane)	0
Ethylbenzene	7
Ethynylbenzene (Phenylacetylene)	10
<i>n</i> -Hexylbenzene	0
Isobutylbenzene	10
Isopropylbenzene (Cumene)	6
<i>alpha</i> -Methylstyrene	4
<i>omega</i> -Methylstyrene	10
1-Phenylbutene-2	8
4-Phenylbutene-1	10
<i>n</i> -Propylbenzene	2
Styrene	1
Toluene	3

* *A.M.A. Arch. Ind. Health*, Gerarde, H. W. (April 1959) and unpublished data.

** Hydrocarbon dissolved in an equal volume of olive oil.

sions between chemical constitution and toxicity for this family of compounds (Gerarde, H. W., 1959 and unpublished data). The hydrocarbons studied and the mortality in 10 rats received

TABLE 15

ORAL TOXICITY OF DI-SUBSTITUTED ALIPHATIC
DERIVATIVES OF BENZENE*

(Male Albino rats, single dose 5 ml kg**)

<i>Hydrocarbon</i>	<i>Mortality in 10 dosed</i>
Di- <i>sec</i> -amylbenzene	0
<i>p</i> -Di- <i>tert</i> -Butylbenzene	0
<i>p</i> - <i>tert</i> -Butyltoluene	10
<i>p</i> -Cymene (<i>p</i> -Isopropyltoluene)	9
<i>m</i> -Diethylbenzene	10
<i>o</i> -Diethylbenzene	10
<i>p</i> -Diethylbenzene	8
<i>p</i> -Diisopropenylbenzene	0
<i>m</i> -Diisopropylbenzene	0
<i>o</i> -Diisopropylbenzene	1
<i>p</i> -Diisopropylbenzene	0
Divinylbenzene	5
Dodecyltoluenes	0
<i>o</i> -Ethyltoluene	10
<i>p</i> -Ethyltoluene	7
<i>p</i> -Isopropenyl- <i>alpha</i> -methylstyrene	0
Vinyltoluene	4
<i>m</i> -Xylene (1,3-Dimethylbenzene)	3
<i>o</i> -Xylene (1,2-Dimethylbenzene)	7
<i>p</i> -Xylene (1,4-Dimethylbenzene)	6

4. *Arch. Ind. Health*, Gerarde, H. W. (April 1959) and unpublished
hydrocarbon dissolved in an equal volume of olive oil.

The dose of 5 ml per kilogram of body weight are shown
Tables 14, 15 and 16.

The benzene derivatives with a single unbranched side
chain the oral toxicity is maximal with two carbons in the side

TABLE 16
ORAL TOXICITY OF MULTI-SUBSTITUTED ALIPHATIC
DERIVATIVES OF BENZENE*
(Male Albino rats, single doses 5 ml/kg**)

<i>Hydrocarbon</i>	<i>Mortality in 10 dosed</i>
Diethyldiisopropylbenzenes (mixture)	8
1,3-Diethyl-5-methylbenzene	6
2,4-Dimethylstyrene	2
2,5-Dimethylstyrene	9
1,3-Dimethyl-5- <i>tert</i> -butylbenzene	8
Durene (1,2,3,4-tetramethylbenzene)	0
Hemimellitene (1,2,3-trimethylbenzene)	10
Hexaethylbenzene	0
Hexamethylbenzene	9
Mesitylene (1,3,5-trimethylbenzene)	1
Pseudocumene (1,2,4-trimethylbenzene)	3
Triethylbenzenes (mixture)	8
Triisopropylbenzenes (mixture)	0
1,3,5-Triisopropylbenzene	0
2-Vinylmesitylene	10

* *A.M.A. Arch. Ind. Health*, Gerarde, H. W. (April 1959).

** Hydrocarbon dissolved in an equal volume of olive oil.

chain as shown in Fig. 31. As the side chain lengthens, the water solubility diminishes rapidly (see Fig. 16, p. 26). This tends to decrease the rate of absorption from the gastro-intestinal tract, which lowers the oral toxicity. Other changes in physical properties, such as viscosity, surface tension and vapor pressure, which accompany the changes in length of the side chain also influence the pharmacological and toxicological properties of the hydrocarbon. Viscosity and surface tension have a marked effect on the rate of absorption of chemicals from the gastro-intestinal tract (Sollman, T., 1957). The pulmonary elimination of hydrocarbons is dependent on vapor pressure as shown

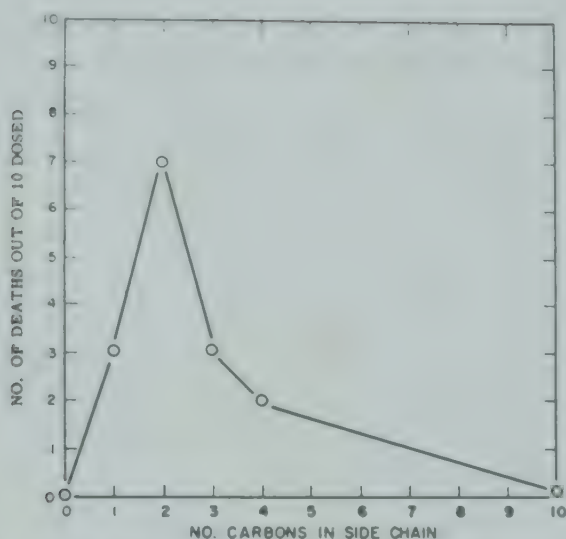


Fig. 17. Effect of length of side chain on acute oral toxicity of mono-n-alkyl derivatives of benzene in the rat. (Gerarde, H. W., 1959).

factor 17. Another important factor influencing toxicity is the rate of biotransformation ("detoxification") of the hydrocarbons to water-soluble metabolites. The combination of the physical and biochemical properties of ethylbenzene makes it the most

TABLE 17

PULMONARY ELIMINATION OF HYDROCARBONS IN THE RABBIT*

Hydrocarbon	Vapor pressure at 40° (mm Hg)	% of oral dose eliminated as hydrocarbon in 3 days
Ethylbenzene	181.08	43
Propylbenzene	59.1	18
Styrene	20	—
Isopropylbenzene	10	> 5
Isobutylbenzene	> 10	> 5
tert-Butylbenzene	> 5	> 2
Acetylene	—	2
Ethylacetylene	—	30

* J. A. Arch. Ind. Health, Gerarde, H. W. (April 1959).

toxic of the mono-*n*-alkyl derivatives of benzene by the oral route of administration for the male Albino rat.

Another generalization that can be made about the mono-substituted alkylbenzenes is that branching of the side chain

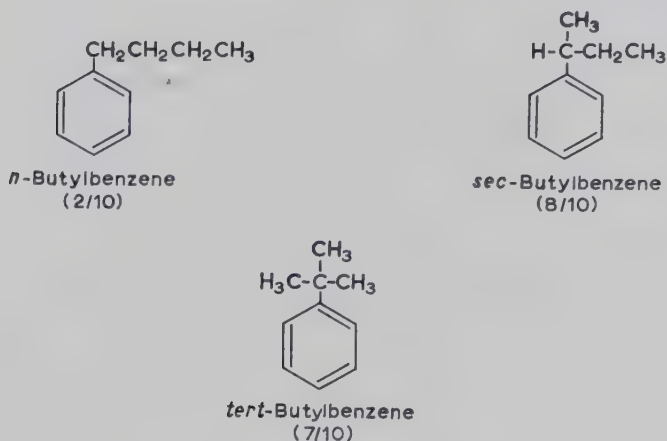


Fig. 32. Branching of side chain increases oral toxicity of isomers of butylbenzene. The figures in parenthesis indicate the number of deaths out of 10 dosed (rats); 2.5 ml 1:1 v/v hydrocarbon in olive oil.

(Gerarde, H. W., 1957)

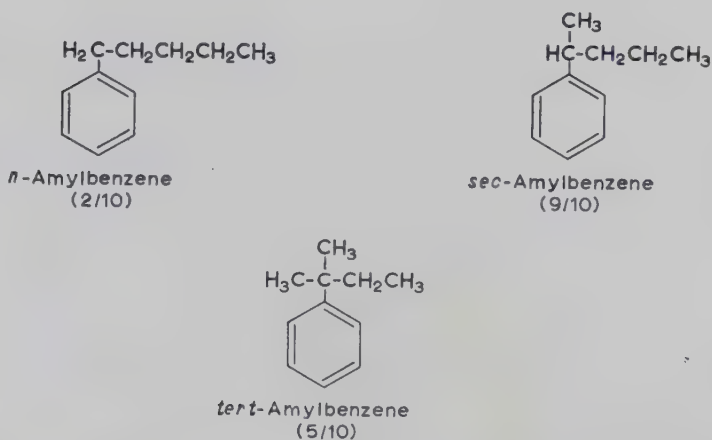
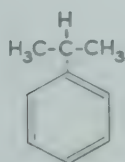


Fig. 33. Branching of side chain increases oral toxicity of isomers of amylbenzene. The figures in parenthesis indicate the number of deaths out of 10 dosed (rats); 2.5 ml 1:1 v/v hydrocarbon in olive oil.

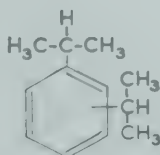
(Gerarde, H. W., 1957)

increases the toxicity. Striking differences in mortality between straight chain and the branched chain isomers of butylbenzene and amylbenzene are shown in Fig. 32 and 33. In general, the branched chain isomer has a more pungent and irritating odor than the corresponding isomer with a straight chain.

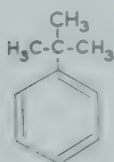
An important factor which may account for the great difference in toxicity between the normal and the branched chain alkylbenzenes is the difference in rate of metabolism. It is known that the unbranched side chain is more readily metabolized than branched alkyl groups. If there is a choice, the enzymes utilize the straight chain and leave the branched chain intact (60). This preference for the straight chain is also shown by microorganisms in the metabolism of sulfonated alkylbenzene detergents. Metabolic studies indicate that microorganisms are



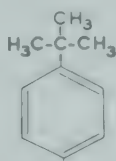
Isopropylbenzene (6/10)



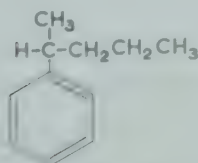
Diisopropylbenzene (0/10)



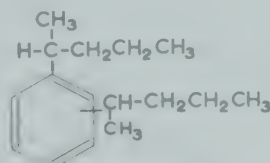
tert-Butylbenzene (7/10)



p-Di-tert-butylbenzene (0/10)



sec-Amylbenzene (9/10)



Di-sec-amylbenzene (0/10)

4. Comparison of acute oral toxicity of mono- and di-alkyl derivatives of benzene. The figures in parenthesis indicate the number of deaths out of 10 fed (rats): 2.5 ml 1:1 v/v hydrocarbon in olive oil.

(Gerarde, H. W., 1959).

able to degrade the *n*-alkyl side chain more readily than branched chain. The foaming in sewage disposal plants is believed to be related to the inability of the microbial flora to degrade the detergents at a sufficiently rapid rate to prevent their accumulation.

Fig. 34 shows that alkylbenzenes containing two branched alkyl groups are much less toxic than the corresponding mono-substituted alkyl derivatives of benzene. A possible explanation for this difference is that the rate of absorption of the di-alkylbenzenes from the gastrointestinal tract is slower than the rate of absorption of the mono-branched chain alkylbenzenes. Furthermore, the former are also less irritating than the latter. There is no evidence that the branched di-alkylbenzenes are more readily metabolized than the corresponding mono-alkylbenzenes to account for the lower toxicity of the di-alkylbenzenes.

TABLE 18
PRINCIPAL POSITIVE PATHOLOGICAL FINDINGS IN
ALKYL- AND ALKENYLBENZENE-DOSED RATS*
(2.5 ml of hydrocarbon 1:1 v/v in olive oil)

<i>Tissue</i>	<i>Gross findings</i>
Lungs	Hyperemic, hemorrhagic
Thymus	Focal hemorrhage
Heart	Cor pulmonale
Adrenal	Hyperemic, hemorrhagic
Spleen	Enlarged, congested
Liver	Enlarged, congested, fatty, hepatitis
Kidney	Congested
Bladder	Distended, petechial hemorrhage
Brain	Hyperemic, congested, focal hemorrhage
Spinal	Hyperemic, congested, focal hemorrhage
Blood	Leukocytosis
Stomach & intestines	Hyperemia

* *A.M.A. Arch. Ind. Health*, Gerarde, H. W. (April 1959).

The principal causes of death in the animals dosed with alkylbenzenes are respiratory paralysis, pulmonary edema and hemorrhage or a combination of these factors. Severe lung hemorrhage is often associated with hemorrhage in other tissues such as the thymus, adrenal and bladder. Liver enlargement, which is a common finding in animals dosed with chemicals, is frequently found in animals dosed with these hydrocarbons. Liver hypertrophy is presumably compensatory for the metabolic stress imposed on the liver by the foreign chemicals. Spleen is usually normal in size or enlarged and the thymus is not involuted. This is in marked contrast with the effects produced by benzene on the hemopoietic tissues, including bone marrow. The principal positive pathological changes found in these animals are shown in Table 18. The generalized dilatation, congestion, hyperemia and hemorrhage is indicative of extensive endothelial injury in these tissues.

Chronic toxicity

Chronic toxicity studies have been conducted on animals with aromatic hydrocarbons used in industry principally to establish safe levels for repeated exposure. For the alkyl derivatives of benzene, particular attention has been directed to the effects of repeated exposure on the blood-forming tissues. Details of the concentrations used, the number and species of animals and the general methodology can be obtained by referring to the aromatic hydrocarbons in Chapters 7 to 11.

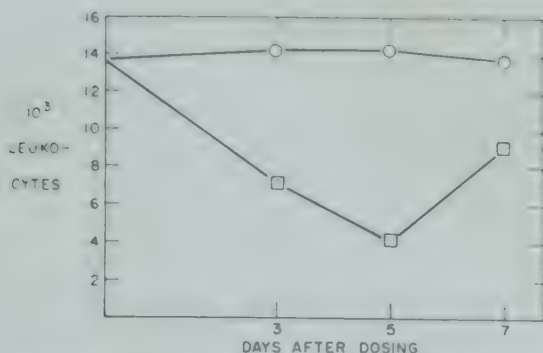
Benzene is considered to be a dangerous chemical because of its insidious destruction of blood-forming tissue. Because benzene is less irritating than the short chain alkyl derivatives, chronic injury due to repeated exposure may occur at air concentrations below levels which warn of its presence.

Animal experimentation conducted by a number of investigators (Fabre, R., and Truhaut, R. (1954), Wolf, M. A. *et al.* (1954), Hine, C. H. *et al.* (1954), Gerarde, H. W. (1956, 1959)) with various alkyl derivatives of benzene clearly indicate that

benzene is unique among hydrocarbons in its myelotoxic potency. It appears that any change in the benzene ring (hydrogenation, halogenation, alkylation, sulfonation, nitration, etc.) results in a loss of the specific myelotoxic potency of the benzene molecule. Possible explanations for the blood dyscrasias occasionally reported in workers exposed to alkyl derivatives of benzene are (1) contamination of these hydrocarbons with benzene, (2) difference in species susceptibility, (3) idiosyncrasy. Benzene is a common contaminant of aliphatic and aromatic hydrocarbon solvents (see Chapter 13, p. 276). Commercial toluene and xylene solvents suspected of causing bone-marrow injury in humans were subsequently shown to contain benzene in considerable proportion. Chronic toxicity studies with the alkyl derivatives of benzene have been conducted with a number of animal species, viz. mice, rats, rabbits, guinea pigs, dogs and monkeys. In view of the uniformity of the response in the different animal species it is highly improbable that the alkylbenzenes are specific myelotoxicants for man. The extensive human experience with these hydrocarbons in recent years provides strong confirmatory evidence. In a review of 39 cases of aplastic anemia, more than 40% were regarded as idiopathic. In the remaining cases, the possible causative agents included a wide spectrum of common drugs and household chemicals (Scott, J. L. *et al.*, 1959).

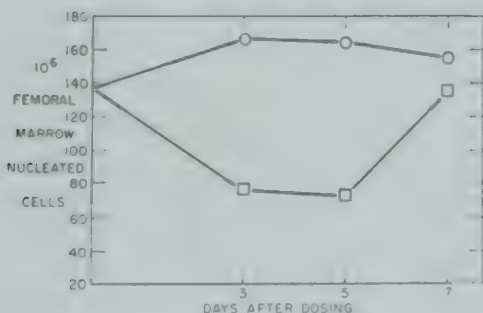
The mechanism of the myelotoxic action of benzene is not known. It is tempting to postulate that the metabolites of benzene are responsible for the cyto-toxicity rather than the hydrocarbon molecule since phenols are known to be 'general protoplasmic poisons'. The quinone intermediates which may be formed in the conversion of benzene to phenols might 'cross-link' the nucleotides during cell division. This would interrupt nucleic acid production and cell formation in blood-forming tissues. The phenols and quinones derived from benzene which have been tested in animals, however, have not been shown to cause myelotoxicity.

distinction is usually made between the acute and chronic toxicity of benzene. The acute is manifested by signs and symptoms of central nervous system involvement, the chronic by evidence of injury to blood-forming tissues. It is important to



35. Effect of single subcutaneous dose of benzene and toluene on leukocyte count in the rat. (2.5 ml 1:1 v/v in olive oil.) \square = Benzene. \circ = Toluene. (Gerarde, H. W., 1959).

emphasize that injury to blood-forming tissue can result from single exposure to benzene as shown in Figs. 35 and 36. The pathological changes in rats 96 hours after a single large dose of benzene were similar to the effects produced after daily dosing with benzene at a level of 1 ml/kg of body weight for 2 weeks (Gerarde, H. W., 1956).



36. Effect of single subcutaneous dose of benzene and toluene on femoral nucleated cell population in the rat. (2.5 ml 1:1 v/v in olive oil.) \square = Benzene. \circ = Toluene. (Gerarde, H. W., 1959).

The anemia caused by naphthalene is due to destruction of the mature erythrocyte, rather than resulting from injury to the blood-forming tissue. The hemolysis observed in naphthalene intoxication has been shown to be due to metabolites of naphthalene. This is discussed further in the detailed discussion of the toxicology and biochemistry of naphthalene in Chapter p. 226.

Biochemistry of the aromatic hydrocarbons

ABSORPTION

The aromatic hydrocarbons are absorbed into the blood stream by inhalation of vapors or mists of the hydrocarbons, following ingestion and injection, and at a much slower rate after topical application to the intact skin. In industry the most important modes of contact are inhalation and skin absorption.

Due to their high lipid solubility, most of the hydrocarbons absorbed in the blood are believed to be bound to the erythrocytes. The fraction present in the plasma is probably dissolved in the micromicrons and or adsorbed on the lipoproteins. The blood concentrations at any particular moment represent the net value

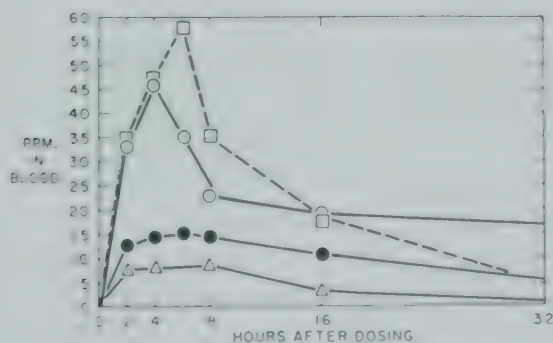


Fig. 27. Concentration of aromatic hydrocarbons in blood of rats after subcutaneous administration of alkyl derivatives of benzene. — □ — Benzene. — ○ — Toluene. ● — Ethylbenzene. — △ — sec-Butylbenzene (2.5 ml 1:1 v/v in olive oil). (Gerarde, H. W., 1959).

between factors favoring absorption into the blood and the forces promoting elimination from the blood stream. Fig. 38 shows the blood absorption-elimination curves for benzene, toluene, ethylbenzene and *sec*-butylbenzene following the su

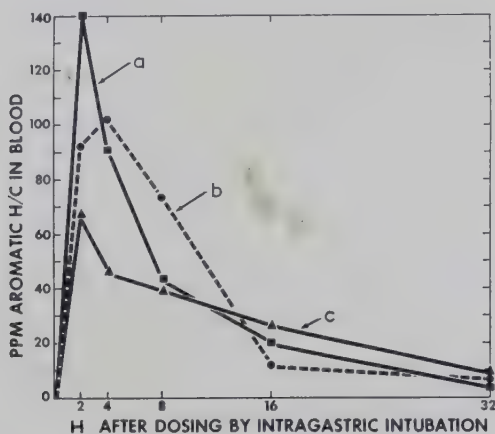


Fig. 38. Effect of diluent on concentration of aromatic hydrocarbons in blood of rats dosed with kerosene by gastric intubation. *a* = 1.25 ml + 1.25 ml mineral oil. *b* = 1.25 ml kerosene. *c* = 1.25 ml kerosene + 1.25 ml olive oil. (Gerarde, H. W., 1955)

cutaneous injection of these hydrocarbons in the rat. The maximum blood levels attained appear to be proportional to the water solubility of the hydrocarbon (see Fig. 16, p. 26). Fig. 38 shows the blood absorption-elimination curve for the aromatic hydrocarbons in kerosene after the oral administration of kerosene to rats. The aromatic hydrocarbons in kerosene are principally mono-methylnaphthalenes, indanes, indenenes, and diphenyls (see Table 56, p. 285). Note the effect of the diluent mineral oil and olive oil on the rate of absorption of the hydrocarbons from the gastrointestinal tract.

The inhibitory effect of olive oil on hydrocarbon absorption is believed to be due to diminished gastric motility which is known to occur after ingestion of fats. Although mineral oil promotes the elimination of the hydrocarbons from the gastro-

estimal tract by virtue of its cathartic action, this results in her peak blood hydrocarbon levels. The relatively rapid passage of the mineral oil-kerosine mixture through the gastro-estimal tract results in simultaneous coverage of a large absorptive mucous membrane surface. This does not occur with olive oil-kerosine mixture which is released slowly through pylorus of the stomach. The significance of this observation from the standpoint of therapy in case of accidental poisoning by ingestion of liquid hydrocarbons is discussed in Chapter 6, 193.

TISSUE DISTRIBUTION

Because of their high lipid solubility, the aromatic hydrocarbons tend to accumulate in the tissues in proportion to their fat content. This is shown by the concentration of toluene in dog

TABLE 19

DISTRIBUTION OF TOLUENE IN ANIMAL TISSUES*

(After Fabre, R. and Truhaut, R.)

(Dogs exposed 180 days, 7.5 to 10 mg/l, 4 h/day, 6 days wk)

<i>Tissue</i>	<i>Toluene (p.p.m.)</i>
Adrenal	20
Cerebellum	19
Bone marrow	18
Brain	18
Liver	14
Blood	9
Kidney	7
Spleen	6.8
Lung	6.6
Thyroid	3.5
Pituitary	1.7

M.A. Arch. of Ind. Health, Gerarde, H. W. (April 1959).

tissues after prolonged exposure by inhalation (Table 19). It is expected that the distribution and accumulation of other aromatic hydrocarbons would have a similar pattern.

EXCRETION

The aromatic hydrocarbons absorbed into the blood are eliminated from the body as unchanged hydrocarbons or as water-soluble urinary biotransformation products conjugated with sulfuric acid, glycine or glucuronic acid. The unchanged hydrocarbons are exhaled through the lungs. A small fraction of hydrocarbon may be excreted in the urine, but this is limited by the solubility of the hydrocarbon in water.

The amount of unchanged hydrocarbon exhaled from the lungs depends primarily on its concentration in the blood and the vapor pressure of the hydrocarbon. The concentration of hydrocarbon in the blood in turn depends on the rate of absorption, storage and biotransformation in the liver and other tissues. A rapid rate of metabolism will tend to keep the blood level down, thus diminishing the rate of escape of unchanged hydrocarbon from the blood into the alveolar air. A slow or inefficient metabolic conversion would have the opposite effect and increase the amount of hydrocarbon passing into the alveoli.

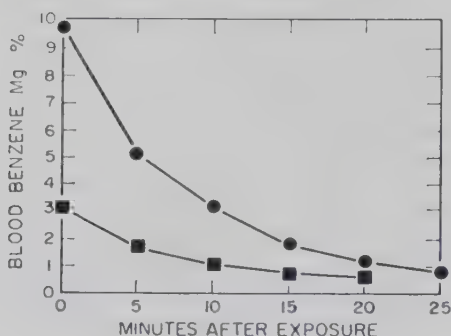


Fig. 39. Elimination of benzene from blood of Guinea pigs after 20 min exposure to benzene vapors. ● = 50 mg/l. ■ = 20 mg/l.

(Péronnet, M., 1933)

Benzene is eliminated rapidly from the blood stream, as shown in Fig. 39. This rapid decrease in blood concentration is due primarily to exhalation of unchanged benzene from the lungs, since the metabolic route of elimination is slow by comparison with the purely physical process of evaporation of hydrocarbon from the blood into the alveolar air.

The alkylbenzenes are eliminated from the blood more slowly than benzene because of their lower vapor pressure, which retards the rate of the non-metabolic route of elimination, as shown in Table 17, p. 59.

The complex polycyclic aromatic hydrocarbons are poorly absorbed from the gastrointestinal tract when added to the diet when administered in a single dose to the rat. A large proportion of anthracene fed to rats was recovered in the feces (Chang, H., 1943). Naphthalene was completely absorbed from the gastrointestinal tract after feeding a single dose of 200 mg to a rat or incorporating 1% of the hydrocarbon in the diet. The extent of the fecal excretion of polycyclic aromatic hydrocarbons in the rat is shown in Table 20.

TABLE 20

FECAL EXCRETION OF POLYCYCLIC AROMATIC HYDROCARBONS
IN THE RAT*

Hydrocarbon	Percentage of oral dose in feces	
	Single dose 200 mg in starch solution	1% Hydrocarbon in the diet
Naphthalene	10	6
Anthracene	69	83
Benzopyrene	57	42
Pyrene	85	79
1:6-Dibenzanthracene	97	90
Methylcholanthrene	69	67
Nthalene	0	0
anthrene	7	5

*Chang, L. H. (1943).

METABOLISM

The fate of the aromatic hydrocarbons in the animal body has been the subject of numerous investigations extending over a period of more than a century. The biochemist has found considerable fascination in studying the biotransformations of this class of relatively 'inert' chemicals. The details of the metabolism of individual aromatic hydrocarbons of industrial importance are discussed in Chapters 7 to 11.

According to Williams (1947), the following generalization can be made regarding the metabolism of the alkyl derivatives of benzene:

1. When the side chain is a normal alkyl group, *e.g.* methyl, ethyl, *n*-propyl, *n*-butyl, *n*-amyl, bio-oxidation of the side chain to $-\text{COOH}$ or $-\text{CH}_2\text{COOH}$ takes place and no oxidation occurs in the ring. Aromatic acids, their glycine conjugates and possibly intermediate compounds in the oxidation of the

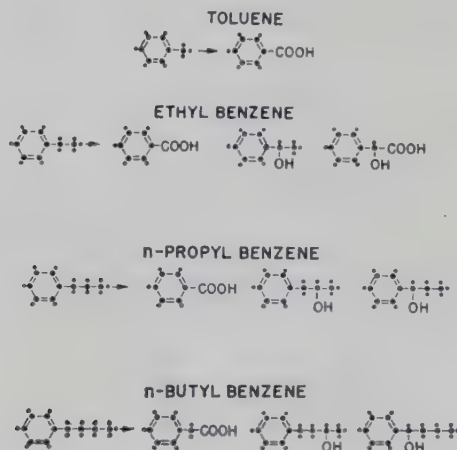


Fig. 40. Biotransformation of mono-alkyl derivatives of benzene in animal (Williams, R. T., 1947)

side chains are excreted. The biotransformations of the *n*-alkyl side chain in methyl, ethyl, *n*-propyl and *n*-butylbenzene are shown in Fig. 40.

2. In the absence of a side chain (*i.e.* benzene), oxidation takes place in the ring as shown in Fig. 41.

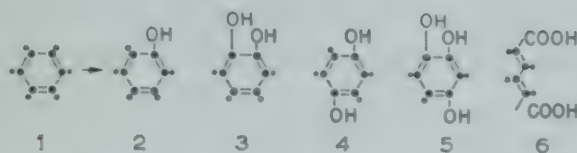


Fig. 41. Principal metabolic transformation products of benzene in the rabbit. From left to right: (1) Benzene, (2) Phenol, (3) Catechol, (4) Hydroquinone, (5) Hydroxy-hydroquinone and (6) Muconic acid. (Williams, R. T., 1947).

3. If a methyl group occurs together with a branched side chain, the methyl group is preferentially oxidized, the ring and the branched side chain being unchanged as shown in Fig. 42 for *p*-cymene (*p*-isopropyltoluene).



Fig. 42. Metabolic transformation of *p*-cymene in the rabbit. (Williams, R. T., 1947).

When more than one methyl group is attached to the ring, only one is oxidized to carboxyl; the others survive passage through the organism as depicted in Fig. 43 showing the biotransformations of *o*-xylene and *m*-xylene in the guinea pig.



Fig. 43. Metabolic transformation of *o*-xylene and *m*-xylene in the Guinea pig. (Williams, R. T., 1947).

Gerarde (1959 b) has found that the administration of *o*- and *p*-diethylbenzene results in the elimination of a blue dye in the urine of male and female rats and hamsters. The sclera, blood

plasma, and tissues are stained a deep blue which persists many days. The rabbit does not excrete a blue urine but the sclera is stained blue after administration of large doses of the chromogenic isomers of diethylbenzene. The guinea pig shows no evidence that these isomers of diethylbenzene are converted

TABLE 21
THE EFFECT OF MONOCYCLIC AROMATIC HYDROCARBONS ON
URINARY SULFATE RATIO (INORGANIC/TOTAL-I/T)
(Rats, single subcutaneous dose *ca.* 5 ml/kg*)

Hydrocarbon	$I/T \times 100$ Hours after dosing			
	24	48	72	96
I. <i>Control (undosed)</i>	86	90	84	73
Benzene**	16	1.3	0	7
II. <i>Mono-substituted</i>				
Toluene	63	78	77	82
Ethylbenzene	89	83	83	73
Styrene (Vinylbenzene)	83	80	85	86
Ethynylbenzene (Phenylacetylene)	91	97	99	99
<i>n</i> -Propylbenzene	80	81	89	85
Isopropylbenzene (Cumene)	84	88	89	82
Allylbenzene (γ -Phenylpropylene)	78	79	84	84
α -Methylstyrene (β -Phenylpropylene)	89	79	86	90
<i>n</i> -Butylbenzene	79	73	91	81
Isobutylbenzene	86	83	93	92
<i>sec</i> -Butylbenzene	82	62	89	84
<i>tert</i> -Butylbenzene	58	35	53	63
1-Phenylbutene-2	68	68	74	59
4-Phenylbutene-1	85	84	89	73
<i>n</i> -Amylbenzene	76	80	83	76
<i>sec</i> -Amylbenzene	77	79	77	77
<i>tert</i> -Amylbenzene	91	79	66	86
<i>n</i> -Hexylbenzene	78	83	84	71
1-Phenyldodecane	91	88	89	93

TABLE 21 (continued)

Hydrocarbon	$I/T \times 100$ Hours after dosing			
	24	48	72	96
<i>Di-substituted</i>				
<i>o</i> -Xylene**	75	72	74	82
<i>m</i> -Xylene	38	66	47	59
<i>p</i> -Xylene	90	79	80	86
<i>o</i> -Ethyltoluene**	86	92	89	89
<i>o</i> -Diethylbenzene**	83	93	87	95
<i>m</i> -Diethylbenzene**	86	82	85	94
<i>p</i> -Diethylbenzene	78	81	87	83
<i>x</i> -Divinylbenzene	81	78	78	82
<i>p-tert</i> -Butyltoluene	98	99	99	97
<i>o</i> -Diisopropylbenzene**	41	38	45	42
<i>m</i> -Diisopropylbenzene	81	83	78	81
<i>p</i> -Diisopropylbenzene	96	83	99	90
1,4-Diisopropenylbenzene	78	77	80	83
<i>Multi-substituted</i>				
1,2,3-Trimethylbenzene (Hemimellitene)	78	69	72	79
1,3,5-Trimethylbenzene (Mesitylene)	53	58	71	75
1,2,4-Trimethylbenzene (Pseudocumene)	74	77	90	83
2,4-Dimethylstyrene	64	55	81	83
2,5-Dimethylstyrene	67	60	82	88
1,3-Dimethyl-5- <i>t</i> -butylbenzene	83	89	98	82
Triethylbenzene** (mixture)	87	90	99	88
1,3,5-Triisopropylbenzene	87	91	87	86
1,2,4,5-Tetramethylbenzene (Durene)	95	88	91	91
2-Vinylmesitylene	81	93	95	91
Diethyldiisopropylbenzene**	85	79	68	69

Gerarde, H. W. (unpublished data).

Produces colored urine.

blue urinary metabolites. The *p*-isomer of diethylbenzene not chromogenic in the rat, hamster, guinea pig or rabbit.

The blue pigment has not been characterized chemically, contains phenolic groups (bound to sulfuric acid) and glucuronic acid. The dye changes to a yellow color at pH above 7.5. The isomerides of diethylbenzene which are chromogenic incre

TABLE 22
THE EFFECT OF DICYCLIC AROMATIC HYDROCARBONS
ON URINARY SULFATE RATIO
(Inorganic/total-I/T)
(Rats, single subcutaneous dose *ca.* 5.0 ml/kg)*

<i>Hydrocarbon</i>	<i>I/T × 100</i> <i>Hours after dosing</i>		
	24	48	72
Indane**	65	19	58
Indene**	62	21	35
Tetrahydronaphthalene (Tetralin)**	17	3	3
Phenylcyclohexane	60	60	65
Phenylcyclohexene	73	74	76
Benzylcyclohexane	79	78	87
Diphenyl**	1.5	11	5
Diphenylmethane**	39	3	19
4-Isopropylbiphenyl	92	34	52
Amylbiphenyl	76	76	81
1-Methylnaphthalene**	89	2	40
2-Methylnaphthalene**	57	14	65
1-Ethylnaphthalene**	68	18	37
2-Ethylnaphthalene**	75	8	68
1,6-Dimethylnaphthalene	93	52	92

* Gerarde, H. W. (unpublished data).

** Produces colored urine.

the total quantity of urinary ethereal sulfate. This indicates that the hydroxylation of the benzene ring has taken place. Tables 21 and 22 show the effect of some monocyclic and dicyclic aromatic hydrocarbons respectively on the urinary sulfate ratio in rats dosed subcutaneously with the hydrocarbons.

The metabolism of specific hydrocarbons of industrial importance and certain polycyclic aromatic hydrocarbons is discussed in Chapters 7 to 12.

The metabolism of acenaphthene is of particular interest be-

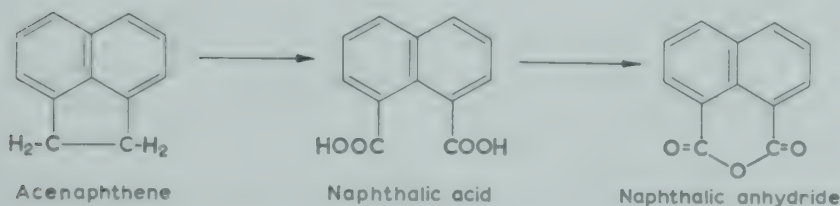


Fig. 44. Biotransformations of acenaphthene in animals.

(Chang, L. H. and Young, L., 1943).

cause it contains a five membered ring similar to that found in the carcinogenic hydrocarbons cholanthrene and 20-methylcholanthrene. Fig. 44 shows that the five-membered ring in acenaphthene is opened by oxidation of the methylene carbons to conjugable carboxylic acid groups. These methylene groups can be regarded as 'potential centers for conjugation' analogous to the side-chains in the alkyl derivatives of benzene and naphthalene (Thorpe, W. V., 1950). It is probable that cholanthrene may undergo the same biofission of the five membered ring demonstrated to occur in acenaphthene.

According to Williams (1947), two tentative generalizations can be made regarding the metabolism of diphenyl and stilbene derivatives, viz.

1. When the number of carbon atoms separating the two benzene rings is 0 or 1, oxidation occurs in the *p*-position in the ring.

2. When the number of carbon atoms separating the phenyl groups is 2, as in stilbene or diphenylhexadiene, oxidation occurs in the *p*-position in both rings. These changes are illustrated in Fig. 45.

The biotransformations of diphenyl are described in Chapter 11.

Triphenylmethane, $(C_6H_5)_3CH$ is excreted in the urine as the unchanged hydrocarbon according to the studies reported by Miriam *et al.* (1927). 35.5% and 27.5% of the oral dose of triphenylmethane administered to rabbits and dogs respectively.

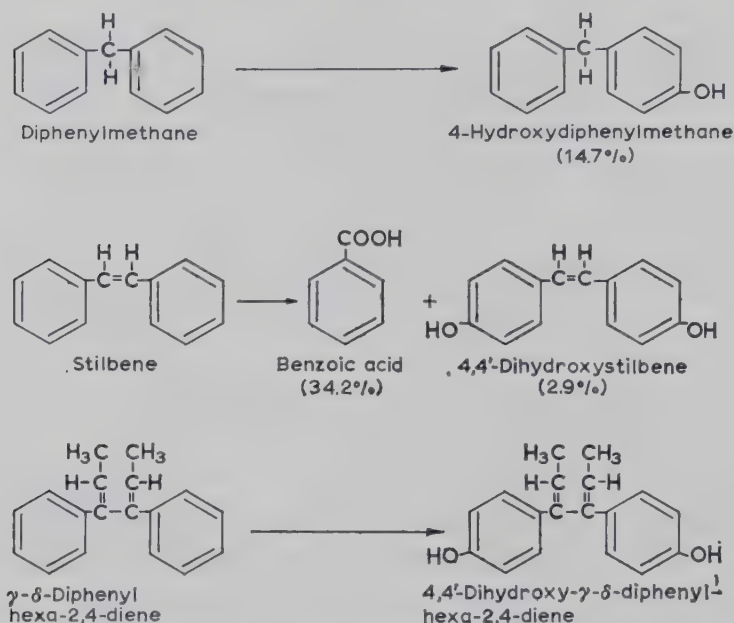


Fig. 45. Biotransformations of diphenylmethane, stilbene and diphenyl hexadiene in rabbits. (Stroud, S. W., 1939, 1940)

was recovered in the urine as the hydrocarbon. The major fraction of the dose of the hydrocarbon is probably metabolized to water-soluble hydroxy derivatives. These have not been identified.

Prevention, detection and treatment of exposure to aromatic hydrocarbons

PREVENTION OF EXPOSURE – INDUSTRIAL HYGIENE

Toxicity vs. hazard

A truism 'Prevention is better than cure' is the basic principle of industrial hygiene. If the exposure or contact with a chemical is kept below the 'effective dose', injury cannot result regardless of the toxicity of a chemical.

The 'toxicity' of a chemical is defined as its capacity for producing injury. This capacity can be determined quantitatively so that it is possible to compare the 'acute' toxicity of one chemical with another or the toxicity of the same chemical by various routes of administration. The term LD-50 signifies the lethal dose of liquids or solids per kilogram of body weight of 50% of the animals dosed. The LC-50 is the concentration of a gas which is fatal to half of the animals exposed for a specified time interval. These terms are quantitative expressions of the toxicity in which mortality is the sole criterion measured. The term ED-50 (effective dose for 50% of the subjects tested) is a more general quantitative expression of acute effects which may or may not be 'toxic' effects.

In industrial toxicology an important distinction is made between 'toxicity' and 'hazard'. Hazard is regarded as the probability that injury will result from the use of a chemical in the quantity and manner proposed. The term carries the connotation of 'risk' or 'chance'. Etymologically the word is of Arabian

origin, *al-zahr* meaning *a die*. An old game of chance played with dice was called hazard.

The hazard associated with the use of a chemical depends on

1. The toxicity of the substance.
2. Its physical state under the conditions of use (solid, liquid or gas).
3. How much is being used.
4. The manner of use, which determines the dose and the portal of entry.

A pint of benzene in the hands of a 'bull in the china shop' may be much more hazardous than a barrel of benzene properly handled by an experienced cautious worker. When the amount of benzene used is one drop, the hazard is practically nonexistent even for the 'bull in the china shop'. The important thing is not how much is used but how much goes 'onto and into the user'. The amount that may safely go 'onto and into' varies with each chemical. Obviously, if this amount is held at zero by proper handling there is no hazard in working with a chemical.

In actual practice it is impracticable, unnecessary and may be impossible for the user to avoid all contact with chemicals. The practical approach is to 'keep exposure to a minimum'. This can be accomplished by 'good housekeeping' and careful handling on the part of the individual user, and in the plant by employing industrial hygiene methods. From the standpoint of industrial hygiene, engineering controls should be designed into the plant before it is built. After the plant is in operation, periodic industrial hygiene surveys should be conducted to make certain that the plant is a safe place to work in 8 h a day, 5 days a week during the worker's normal, productive lifespan.

B. Threshold limits

The terms 'threshold limit', maximum allowable concentration (MAC), maximum acceptable concentration, recommended maximum concentration, and maximum permissible concentration

are used to describe the concentration of an atmospheric aminant which should cause no significant impairment of health of the large majority of workers even after repeated our daily exposure.

he most widely used threshold limits are those published ually by the Committee on Threshold Limits of the American ference of Governmental Industrial Hygienists (ACGIH). definition of threshold limit given by the ACGIH Committee 955 is as follows. 'The maximum average atmospheric con- ration of contaminants to which workers may be exposed an eight-hour day without injury to health.'

he threshold limits (ACGIH) for aromatic hydrocarbons d in industry are shown in Table 23.

TABLE 23

THRESHOLD LIMITS FOR AROMATIC HYDROCARBONS

American Conference of Governmental Industrial Hygienists, 1959)

<i>Hydrocarbon</i>	<i>p.p.m.</i>	<i>mg/m³</i>
Benzene	25	80
<i>p-tert</i> -Butyltoluene	10	60
Ethylbenzene	200	870
<i>o</i> -Methylstyrene	100	480
Styrene	10	60
Toluene	200	750
Vinyltoluene	100	480
Xylene	200	870

he information used in establishing the threshold limits of aromatic hydrocarbons was obtained from:

Laboratory studies using experimental animals.

Laboratory tests using human subjects.

Field investigations which combine environmental and clinical data.

Combination of the first three methods.

In 1927 Winslow first proposed for benzene a limit of 1 p.p.m., based on extensive examination of exposed workmen and animal inhalation data. As additional data became available the threshold limit was lowered to its present value of 25 p.p.m. (80 mg/m³). It must be emphasized that considerably high concentrations of benzene can be tolerated without causing excessive discomfort. The absence of mucous membrane irritation combined with the presence of serious systemic injury to blood-forming tissue has stigmatized benzene as the most dangerous aromatic hydrocarbon used in industry.

The threshold limits of the alkyl derivatives of benzene, in contrast with benzene, are based primarily on the effects of their vapors on mucous membranes rather than systemic intoxication resulting from absorption of the hydrocarbons. The alkylbenzenes, in general, are more irritating to mucous membranes and have a stronger effect on the chemical senses than benzene. This irritative quality makes them 'self-policing' or 'self-monitoring' which makes insidious systemic intoxication less likely to occur. The vapors of most alkylbenzenes are disagreeable and unpleasant at concentrations well below the levels capable of causing adverse systemic effects in experimental animals.

The threshold limits do not represent fine lines between safe and dangerous concentrations. Although a single concentration figure is assigned to each hydrocarbon, this number should not carry the connotation of mathematical preciseness that is usually associated with numbers. The number actually represents a concentration zone or band varying in width with each chemical. The extent to which the threshold limit can be exceeded for short, repeated exposures depends on the characteristics of the hydrocarbon. In the case of benzene the level of 25 p.p.m. should be a firm upper limit in view of the fact that the value is based on serious systemic intoxication resulting from absorption of the hydrocarbon. In the case of the alkyl derivatives of benzene in which the threshold limit is set at a level which will not cause complaints of disagreeable odor, eye and nose irritation, bri

osures to concentrations exceeding the maximum allowable concentrations cause less concern.

One can only speak in generalities as to how long a person may be safely exposed to concentrations exceeding the threshold limit of the aromatic hydrocarbons. The threshold limit should be used as the concentration (C) in Haber's law which states that the concentration (C) of a chemical multiplied by the time of exposure to the chemical (T) is a constant (K):

$$K = C \times T$$

Although it is mathematically correct to say that K (Haber's constant) is equal to the number of molecules of chemical that have been inhaled, this does not mean that the effects produced by this number of molecules are always the same. Haber's constant K is not an index of the effects of this number of molecules because the physiological effects of a chemical depend on the *concentration* of molecules in the blood and tissues at any particular moment, as well as *the total number* of molecules that have entered the blood or organs. A given number of molecules may cause irreparable tissue injury if high concentrations are attained by flooding the blood with the chemical. The same number of molecules may be completely innocuous if the tissue levels are maintained at low concentrations by allowing the same number of molecules to enter the tissues over a longer time interval.

From the foregoing discussion it is apparent that the threshold limits, which have been established for the 8-h working day, should not be applied to the field of air pollution. In addition to the limitations of Haber's law, the setting of standards for chemicals in community air is further complicated by a multiplicity of factors, too numerous to mention here. The pitfalls in using threshold limits in air pollution have been discussed by Schrenk (5).

The Imperial Chemical Industries, Ltd., Industrial Products Health Research Committee has published a table of 'Toxic

Concentrations of Various Gases, Dusts, Fumes and Met in the Atmosphere' which is used extensively in England as a guide to safe atmospheric concentrations of industrial chemicals. This table presents: (1) a combination of concentration and exposure time which may lead to symptoms of illness, (2) combination of concentration and time which will give rise to severe toxic effects, (3) a concentration which serves as a guide to satisfactory working conditions. The latter concentration corresponds to the threshold limits of the American Conference of Governmental Industrial Hygienists. The values appearing in the Imperial Chemical Industries table for the aromatic hydrocarbons are shown in Table 24.

The Soviet Union has also established hygienic standards for maximum allowable concentrations in the working atmosphere. These consist of a single concentration for an 8-h working day.

TABLE 24

<i>Hydrocarbon</i>	<i>Concentrations which will give rise to severe toxic effects in persons exposed to them for the stated times.</i>		
	<i>p.p.m. v/v</i>	<i>mg/m³ (20°)</i>	<i>Time of exposure (minutes)</i>
Benzene (Benzol)	1,500	4,800	60
'Dowtherm A' (Diphenyl) - Dust	—	—	—
Naphtha distillate (as cumene)	300	1,500	60
Styrene	1,000	4,330	60
Toluene (Toluol)	1,000	3,830	60
Xylenes (Xylols)	1,000	4,410	60

* I.C.I. Industrial Products and Health Research Committee, July 1955

general, the threshold limits established by the U.S.S.R. are considerably below the American and British values. The Soviet threshold limit for benzene is 10 p.p.m. and the value for toluene is 20 p.p.m. These values are based primarily on animal investigations in which the Pavlovian conditioned reflex plays an important role. According to Smeljansky (1959) the Pavlov method has made it possible to detect in animals adverse effects to chemicals which are not detectable by other methods. At the present time there are no international standards for maximum allowable concentrations of toxic substances in the working atmosphere. The first international symposium on maximum allowable concentration was held in Prague in April 1958 to discuss definitions, methods, and the possibility of establishing international threshold limits (Deichmann, W. D. and Harde, H. W., 1959).

TOXIC CONCENTRATIONS OF AROMATIC HYDROCARBONS IN THE ATMOSPHERE*

Concentrations, which if exposure to continues for more than a short time may lead to symptoms of illness.

Concentrations in the general atmosphere of the plant greater than those given below indicate unsatisfactory conditions

<i>p.p.m.</i> v/v	<i>mg/m³</i> (20°)	<i>p.p.m.</i> v/v	<i>mg/m³</i> (20°)
500	1,600	50	160
—	—	—	2
150	750	50	250
200	866	100	433
300	1,149	100	383
300	1,323	100	441

C. Preplacement examination

Pre-employment examinations are conducted to determine a record the physical condition of the prospective employee and to assign the worker to a suitable job in which his disability, if any, will not affect his personal efficiency, his safety and health or safety of others (A.M.A. Council on Industrial Health, 1956). The initial health examination should include: (1) Family and personal medical history, (2) Occupational history, (3) Physical examination and (4) Other procedures to help determine the individual's employability and his capacity for work (A.M.A. Reference Committee on Hygiene, Public Health and Industrial Health, 1957). Laboratory and other diagnostic procedures which may be included in the preplacement examination are urinalysis, complete blood examination and chest X-ray.

For maximum protection of the prospective worker and employer the following should not be employed in work which would require actual contact with aromatic hydrocarbons:

1. Persons having organic disease of the heart, lungs, liver and kidney.
2. Individuals with chronic skin disease.
3. Persons giving a history of previous benzene intoxication.
4. Individuals having any evidence of abnormality of the blood picture or blood-clotting mechanism.

DETECTION OF EXPOSURE

A. Exposure tests

Although the practical objective in industrial hygiene is to prevent exposure by the use of proper handling procedures and engineering methods, the ultimate test of the effectiveness of these precautionary measures is the individual exposed to the chemicals. The worker is a continuous biological sampling device whose blood stream is separated from the air he breathes by two endothelial membranes a fraction of a micron in thickness. The pulmonary capillary and alveolar endothelium are readily permeable

ble to vapors and mists containing chemicals so that the pulmonary venous blood is in virtual equilibrium with the air in the lungs. The worker's skin, which is thousands of times thicker than the pulmonary endothelium, may also allow chemicals to enter the blood if the exposure is severe enough. Accidental ingestion of chemicals is an infrequent occurrence in industry but regrettably too common in the home.

The detection of a chemical or its specific metabolites in the tissues or biological fluids of an individual is incontrovertible evidence that the chemical has entered the blood stream. This may serve as a *test for exposure* to the chemical. If the metabolism of a hydrocarbon and the routes of its excretion are known, it is possible to follow the elimination of the hydrocarbon itself or of its metabolites in the expired air, blood or urine. From the amount of eliminated chemical or metabolite it is possible to calculate the amount of hydrocarbon absorbed.

In principle, exposure tests give a more accurate measure of a worker's exposure than actual analysis of the air in the working environment. Exposure tests show that the chemical has been absorbed not only by inhalation but through the skin, the digestive tract or by other routes of administration.

For the aromatic hydrocarbons the detection of the specific hydrocarbon in the breath, blood or urine has found limited application because of the extremely high sensitivity required to detect minute quantities of hydrocarbon present in biological samples. The pulmonary ventilation of unchanged hydrocarbon is an important route of elimination of benzene, toluene and vinylacetylene (see Table 17, page 59). If sufficiently sensitive methods of analysis were available, breath analysis could serve as a test for exposure to these hydrocarbons and hydrocarbons having a comparable vapor pressure (possibly styrene, benzene, xylenes and cumene).

The urinary sulfate ratio has been used as a test for benzene exposure for a number of years. This test and its significance are discussed in detail in Chapter 7 (Benzene). Teisinger and

Bergerová-Fišerová (1955) have reported that phenol excretion in the urine is a reliable test for exposure to benzene. In addition to reliability, the quantitative determination of phenols in the urine is stated to be less time consuming and requiring less technical skill than the determination of inorganic and ether sulfate in the urine. For further discussion of the use of urinary phenol for measuring exposure to benzene see Chapter 7, Benzene.

The urinary benzoic acid excretion has been used as a test for exposure to toluene (Teisinger, J. and Srbová, J., 1955). Benzoic acid is the *in vivo* oxidation product formed from toluene. It is excreted in the urine as hippuric acid, a conjugate of benzoic acid, and the amino acid glycine (see Chapter 8, Toluene).

Benzene and toluene are the only aromatic hydrocarbons for which correlations have been made between the concentration of hydrocarbon in the air and the amounts of urinary metabolites excreted under actual working conditions.

The detection of naphthols in the urine has been used to measure exposure to naphthalene in case of ingestion.

It must be emphasized that the detection of the chemical and/or its metabolites in the breath and biological fluids does not mean that injury has resulted from exposure to the chemical. The odor of ether may be detected on the breath of a patient for as long as 24 h after administration of the anesthetic. This indicates that the individual has been exposed to ether. It does not mean that he is suffering from ether intoxication or injury of any kind due to the ether that has entered the blood stream.

B. Tests for incipient or latent toxicity

It is axiomatic that biochemical injury occurs before there is any evidence of clinical or morphological abnormality resulting from exposure to a chemical. The detection of a 'biochemical lesion' indicates injury at the biochemical level, which will become manifest at the cellular and clinical level if exposure to the chemical is continued.

The best example of a test for incipient toxicity is the decrease in the plasma or erythrocyte concentration of the enzyme acetylcholinesterase following exposure to alkylphosphates. The detection of the 'biochemical lesion' by measurement of the blood cholinesterase concentration has made it possible for men to work with these highly toxic chemicals without danger to health. There is no comparable enzymatic or biochemical test for the detection of incipient toxicity due to the aromatic hydrocarbons. The detection of a slight leukopenia or thrombocytopenia following exposure to benzene is a manifestation of injury to the blood forming tissues. These hematological changes may appear before the advent of symptoms of benzene intoxication. The decrease in leukocyte count indicates that the blood forming tissue is not producing cells at a sufficiently rapid rate to maintain the normal leukocyte population. Clinical experience has shown that severe benzene intoxication may be associated with relatively moderate degrees of leukopenia and thrombocytopenia.

Detailed descriptions of the manifestations of intoxication by specific hydrocarbons are given in Chapters 7 to 11.

Periodic health examination

Periodic health examination is usually provided for workers who are exposed to materials that are definite health hazards or whose work involves the safety of others. Caution dictates that it is advisable to do periodic medical evaluations as a check on the efficiency of the engineering controls. This also enables the physician to detect the hypersusceptible individual and the worker whose personal unsafe practices defeat the control processes.

The frequency of the examination should vary in accordance with the quality of the engineering control, the severity of the exposure and the individual findings on each examination. Some exposures might justify examinations or laboratory tests of the workers on a monthly or quarterly basis, while in other cases

annual or biennial evaluations may be adequate. The industrial hygienist can be a great help to the physician by finding out if a man is actually exposed to chemicals or if he simply walks past barrels of chemicals in the warehouse. The frequency of examination is determined by the industrial physician who should be familiar with the health hazards associated with the chemicals used by the workers and with the working conditions in the plant.

Benzene is unquestionably the most dangerous aromatic hydrocarbon used in industry. A periodic physical examination should be conducted at least once a year on employees working with benzene. Since the other hydrocarbons are not insidiously myelotoxicants and are self-policing because of their effects on mucous membranes, a rigid schedule of annual periodic physical examinations is not so important. It must be emphasized that the frequency of the periodic physical examination depends on the working conditions and the probable degree of exposure. In Italy the law requires a quarterly physical examination of workers engaged in the production of benzene and homologous hydrocarbons and a semi-annual physical examination of workers having direct contact with naphthalene and its homologues. A worker engaged in operations in which there is contact with tar, asphalt, soot, minerals, pitch, and related products suspected of being carcinogenic must be examined semi-annually or immediately if he claims or presents a suspicious neoplastic lesion (Aonzo, E., 1958).

Further details regarding periodic physical examinations for workers having potential exposures to specific aromatic hydrocarbons will be found in Chapters 7 to 11. A protective program for workers having potential exposure to carcinogenic hydrocarbons is described in Chapter 12 (Polycyclic Hydrocarbons).

TREATMENT OF AROMATIC HYDROCARBON INTOXICATION

Acute inhalation intoxication ('Gassing' accidents)

Inhalation of a sufficiently high concentration of the volatile aromatic hydrocarbons (benzene, toluene, xylenes, styrene, ethyl benzene, cymenes, cumene, etc) or solvent mixtures containing hydrocarbons can cause acute intoxication. The signs and symptoms of acute exposure are due to the rapid effects produced on the central nervous system and cardiovascular system. They include excitation, pallor, dizziness, weakness, breathlessness, tightness of the chest, rapid pulse, tremors, cyanosis, convulsions, and loss of consciousness.

The victim of acute inhalation poisoning presenting any of the signs or symptoms described above must be handled as an emergency. He must be removed immediately from the contaminated atmosphere. If natural breathing has been interrupted, artificial respiration must be instituted at once. Oxygen may be administered if it is available. The individual must be kept warm and at complete rest. Since epinephrine is known to sensitize the myocardium to hydrocarbon vapors, it is contraindicated in the treatment of collapse due to acute exposure to hydrocarbons (Chenoweth, M. B., 1946). After normal breathing has resumed, no specific treatment is necessary. However, the patient should be kept under observation for several hours after the acute incident. Treatment beyond this point is supportive and symptomatic. Recovery from the acute episode is usually complete, but it may take several weeks depending on the severity of the exposure. If prolonged cyanosis and anoxia occurred during the acute intoxication, permanent cerebral injury may result from oxygen deprivation (see Chapter 4, p. 50).

Eye contact

In the event of accidental eye contact with liquid aromatic hydrocarbons, the eye should be flushed immediately with water. Eye

fountains designed for use at the site of the accident are excellent but any quick source of water is satisfactory. Dunking the injured person's head in a pail of water and forcing his eyes open may save his sight. This vital first flushing may require the assistance of fellow workers because of pain and spasm of the eyelids. The flushing of the eyes should be continued for at least 15 minutes before the patient is sent to the physician for diagnosis and further treatment. Although ophthalmologists may differ in regard to specific therapy for chemical eye injury, there is complete unanimity on this point: *immediate copious irrigation* is vital *before* the patient is sent to the physician.

C. Skin contact

The aromatic hydrocarbons are not absorbed percutaneously at a sufficiently rapid rate to cause systemic intoxication or penetration of the intact skin. This is in contrast with aniline, for example, which may cause systemic poisoning if only a small area of skin is exposed to the liquid.

In case of skin contact with the aromatic hydrocarbons, direct local cutaneous irritation, drying, and defatting of the skin are minimized by prompt removal with a clean cloth and subsequently washing the affected parts with soap and water. Hydrocarbon solvents should not be used for cleaning the skin. However, the occasional use of kerosene or similar solvent for cleaning a small area of the skin does not cause harmful effects in normal individuals. Clothing that has become contaminated or 'wetted' with aromatic hydrocarbons should be promptly removed. Prolonged contact of the skin with liquid benzene, toluene, styrene, or xylenes may cause blistering. The contaminated clothing should be laundered before it is worn again.

There is no specific treatment for skin irritation or dermatitis resulting from contact with the aromatic hydrocarbons. In normal individuals spontaneous healing begins when contact with the hydrocarbon stops.

Ingestion and aspiration

Oral toxicity of the aromatic hydrocarbons is relatively low. The toxicity of liquid hydrocarbons aspirated directly into the lungs is many times greater than the oral toxicity; the oral LD-50 may be 200 times greater than the intratracheal LD-50. Extensive pulmonary edema and hemorrhage follow the aspiration of a fraction of a milliliter of the liquid aromatic hydrocarbons. Because of the great difference between the oral and the intratracheal toxicity and the attendant hazard of aspiration, the use of vomiting and passage of stomach tubes for gastric lavage are contraindicated. The dilution principle for the treatment of ingested poisons may be safely and effectively employed. The oil tends to diminish the rate of absorption of the aromatic hydrocarbons from the gastrointestinal tract in rats, thus preventing the peaks in blood hydrocarbon levels which may cause tissue injury (see Fig. 38, p. 68).

Unless enormous doses of the liquid aromatic hydrocarbons are ingested, the stomach need not be emptied, and dilution with a vegetable oil is all that is required. If available, more palatable diluents such as ice cream, butter, or cream will serve the same purpose.



Part II

AROMATIC HYDROCARBONS OF
INDUSTRIAL IMPORTANCE

Benzene

Synonyms

Benzol, phenyl hydride, coal naphtha, phene, benzole, cyclohexatriene.

Molecular formula: C_6H_6 .

Structural formula:



Molecular weight: 78.11.

Physical and chemical properties

B.P.: $80.1^{\circ} C$ ($176.2^{\circ} F$) at 760 mm of mercury.

M.p.: 5.4° ($41.7^{\circ} F$) to 5.5° ($41.9^{\circ} F$).

Vapor pressure: 74.6 mm of Hg at 20° ($68^{\circ} F$).

Vapor density (air = 1): 2.77.

Density of saturated vapor-air mixture at 760 mm of mercury (air = 1): 1.22 at 26° .

Per cent in saturated air, 760 mm of mercury: 13.15 at 26° .

Liquid density: 0.899 at 0° ($32^{\circ} F$).

Index of refraction: 1.5016 at 20° ($68^{\circ} F$).

Solubility: Soluble in 1430 parts water; miscible with alcohol, chloroform, ether, carbon disulfide, carbon tetrachloride, glacial acetic acid, acetone.

Flash point: $12^{\circ} F$ (C.C.).

Flammable limits (per cent by vol. in air): 1.35-6.75.

Conversion factors (25° and 760 mm mercury): 1 mg/l vapor = 313 p.p.m., 1 p.p.m. of vapor = 0.00319 mg/l.

Sources, used and probable modes of contact

Benzene is a petrochemical and a by-product of the coke-oven industry (see Chapter 1). From coke-oven operations it is recovered from the gases and coal tar. In the petroleum industry benzene is manufactured from catalytically reformed liquid naphthas from which it is isolated by distillation or solvent extraction.

Benzene is used extensively as a solvent in the chemical and drug industry, as a component of motor fuels, and as a starting material for synthesis of numerous chemicals. Some of the chemicals derived from benzene are: styrene, phenol, aniline, DDT, chlorobenzene, isopropylbenzene (cumene), nitrobenzene, diphenyl, cyclohexane, adipic acid, detergents and many others.

Benzene has a considerable vapor pressure at room temperature (74.6 mm at 20°) and consequently the most likely mode of contact is by inhalation of vapors. Direct skin contact with the liquid is also a possibility as a result of leaks or accidental spills.

Analytical methods

The concentration of benzene in air may be determined with the direct reading field equipment described in Chapter 1. Maffett *et al.* (1956) have described a rapid, direct procedure for the collection and spectrophotometric determination of microquantities of benzene in air.

Colorimetric chemical methods based on nitration and color formation with sulfuric acid-formaldehyde mixture may also be used for analysis of 'grab' air samples or after passing air through suitable collecting media. These chemical methods may also be used for the determination of benzene in blood, urine and tissues following preliminary separation of the hydrocarbon from the sample by distillation and/or extraction. An ultraviolet spectrophotometric method has been described for the determination of benzene in air.

photometric method has recently been described for the analysis of benzene in blood (Guertin, D. and Gerarde, H. W., 1959).

Toxicology

Acute toxicity

Liquid benzene on direct contact with the skin may cause erythema and blistering. Skin contact with benzene removes fat from the tissue which may result in the development of a dry, flaky dermatitis if exposure is repeated or prolonged. Benzene is poorly absorbed through the intact skin so that systemic intoxication from the percutaneous absorption of benzene is unlikely to occur. Immersion of the hands and forearms in benzene for 25 to 35 minutes produced no evidence of skin absorption as evidenced on urine analysis for ethereal sulfate (Conca, G. L. and Maltagliati, A., 1955). The direct aspiration of liquid benzene into the lungs causes immediate pulmonary edema and hemorrhage at the site of contact with the pulmonary tissue (Gerarde, H. W., unpublished observation).

The ingestion of liquid benzene causes local irritation of the mucous membranes of the mouth, throat, esophagus and stomach. The subsequent absorption of ingested benzene into the blood leads to signs and symptoms of systemic intoxication. The ingestion of a tablespoonful (about 15 ml) of benzene has been known to cause collapse, bronchitis and pneumonia. Liquid benzene has been used as a drug for the treatment of chronic myelocytic leukemia. It was administered in capsules diluted in olive oil. The initial daily dose of 2 g, given orally in four doses of 0.5 g each, was increased gradually in one week to a maximum of 4 or 5 g daily. Gastrointestinal distress was minimized by the ingestion of large quantities of fats, such as butter. Side effects regarded as an indication for discontinuation of therapy were headache, vertigo, bladder irritability, impotence, and other disturbances and evidence of renal congestion (Wintrobe, M., 1946).

High concentrations of benzene vapor are irritating to the

mucous membranes of the eyes, nose and respiratory tract. The inhalation of a high concentration of benzene vapor may cause exhilaration followed by drowsiness, fatigue, dizziness, headache and nausea. The pulse rate increases, there may be a sensation of tightness in the chest accompanied by breathlessness and ultimately the victim may lose consciousness. Convulsions and tremors occur frequently and death may follow in a few minutes or several hours following severe exposure. The response of the rabbit to brief exposures to high vapor concentrations of benzene is shown in Table 25. Epinephrine is known to sensitize the

TABLE 25
RESPONSE OF RABBITS EXPOSED TO 35,000-45,000 P.P.M.
BENZENE VAPOR*

<i>Average time for occurrence (minutes)</i>	<i>Response</i>
3.7	Light anesthesia
5.0	Excitation-running-tremors
6.5	Loss of pupillary reflex to strong light
11.4	Loss of blink reflex
15.6	Involuntary blinking
36.2	Death

* After Carpenter, C., *et al.*, 1944.

myocardium to the action of benzene and ventricular fibrillation may be induced. Post-mortem findings in cases of acute benzene exposure include extensive petechial hemorrhage in the brain, pleurae, pericardium, urinary tract, mucous membranes and skin. There are no specific lesions pathognomonic of acute benzene intoxication.

Recovery from an acute exposure to benzene depends on the severity of the exposure. Breathlessness, nervous irritability and unsteadiness in walking may persist in severe cases for two or

three weeks. Chronic effects of acute benzene intoxication may arise and persist long after the acute incident.

The relationship between benzene air concentrations and physiological effects produced in man are shown in Table 26.

TABLE 26
EFFECTS OF BENZENE VAPOR ON MAN

<i>Air concentration p.p.m.</i>	<i>mg/l</i>	<i>Duration of exposure (minutes)</i>	<i>Effects</i>
0,000-19,000	65-61	5-10	Fatal
7,500	25	30	Dangerous to life
3,000	9.6	30	Endurable
1,500	4.8	60	Serious symptoms
500	1.6	60	Symptoms of illness
50-50	0.48-0.16	300	Headache, lassitude, weariness
5 (MAC)*	0.08	480	None

MAC = Maximum allowable concentration (Threshold limit).

Exposure to concentrations exceeding the threshold limit should not be permitted without suitable respiratory protection.

Chronic toxicity

The effects of inhaling small quantities of benzene vapor over prolonged period of time are of the greatest importance in the industrial use of this hydrocarbon. These effects are due to the insidious injury to the blood-forming tissue at atmospheric concentrations which may not cause irritation of mucous membranes or any unpleasant sensory effects. The threshold limit for benzene in the working atmosphere has been lowered recently to the present value of 25 p.p.m. There are two well-documented cases of chronic benzene intoxication due to repeated exposure to 75 p.p.m. of benzene in the working environment (Bowditch, M., and Elkins, H. B., 1939).

Early symptoms of chronic exposure to benzene vapors are varied and vague and not specific for benzene exposure. They may consist of headache, fatigue, dizziness, and loss of appetite. As the condition progresses more specific signs of benzene intoxication become manifest, such as bleeding from the nose, the gums and mucous membranes and the development of purpuric spots and ecchymoses of the skin at the site of injury. The individual may complain of shortness of breath and appear to be anemic. In addition, there may be a slight elevation in temperature, a rapid pulse and a low blood pressure.

The most common abnormalities in the blood of workers exposed to benzene are anemia and leukopenia, the latter believed by many authorities to be the earliest sign of chronic benzene intoxication. Macrocytosis and thrombocytopenia are also frequently present in benzene poisoning. The classical picture of severe anemia, leukopenia, and thrombocytopenia is found in the severe and fatal cases of aplastic anemia following benzene exposure. Leukocytosis, eosinophilia, and the presence of immature marrow cells in the circulating blood have also been reported. Elevated serum bilirubin found in some cases of benzene intoxication indicates increased red blood cell destruction. The bone marrow may be aplastic or hyperplastic and does not always correlate with the peripheral blood findings indicating hypo- or hyperactivity of the blood forming tissue. Splenomegaly associated with extramedullary hemopoiesis and myeloid leukemia have been reported in a few cases.

It is important to emphasize that there are great variations in the susceptibility to benzene intoxication and that there is no 'typical' blood picture. Chronic benzene intoxication may appear after a few weeks or many years of exposure, or even many years after the actual exposure to benzene has ceased and may prove fatal.

The effects of benzene on the blood-forming tissue have been repeatedly demonstrated in animal experiments with mice, rats, rabbits and dogs. On the basis of the studies with benzene and a

number of alkyl derivatives it appears that benzene is unique among hydrocarbons as a bone-marrow toxicant (Gerarde, H. V., 1959). The mechanism of action of benzene as a myelotoxin is not known. Although it is tempting to postulate that the myelotoxicity of benzene may be related to its metabolic pathway, there is no experimental proof for this. Details of the metabolism of benzene are discussed in the section on biochemistry. Prolonged skin contact with liquid benzene will remove the natural fats from the skin, and may culminate in dermatitis. Although small amounts of benzene are undoubtedly absorbed through the skin it is highly improbable that systemic intoxication could result from the percutaneous route of administration through the intact skin. Dermatitis due to benzene indicates that poor working conditions exist which should be investigated, not only because of the dermatitis but because systemic intoxication may result from the inhalation of benzene vapors.

Biochemistry

Benzene is rapidly absorbed into the blood by ingestion, injection and inhalation. Because of its lipid solubility benzene tends to accumulate in tissues in proportion to their fat content (see Table 19, p. 69). Due to its high vapor pressure at body temperature benzene is rapidly eliminated from the blood as shown in Fig. 39, page 70. About 40% of a single oral dose of benzene administered to the rabbit is eliminated from the lungs as unchanged hydrocarbon within the immediate 72-hour period after dosing. A very small fraction of the oral dose of benzene is eliminated unchanged in the urine. Most of the benzene is converted by the liver into water-soluble metabolites which are eliminated in the urine conjugated with glycine, glucuronic acid or sulfuric acid. The elimination and the principal biotransformation products of benzene in the rabbit are shown in Fig. 46.

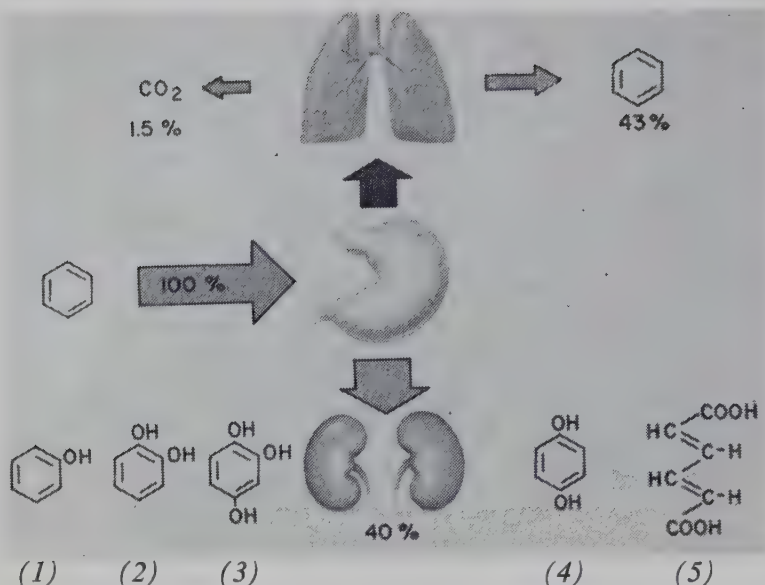


Fig. 46. Elimination and biotransformation of benzene in the rabbit in the 72-hour interval after a single oral dose. Principal urinary metabolites are, left to right: (1) Phenol, (2) Catechol, (3) Hydroxy-hydroquinone, (4) Hydroquinone, (5) Muconic acid. (Williams, R. T., 1947).

Threshold limit

The threshold limit or maximum allowable concentration (MAC) for benzene in the working environment for an 8-hour work day is 25 p.p.m. (American Conference of Governmental Industrial Hygienists, 1959).

Prevention, detection and treatment of exposure

(A) Prevention

Individuals working with benzene should be particularly careful to avoid all possible exposure to the vapors or skin contact with the liquid hydrocarbon. Laboratory procedures requiring the use of benzene should be conducted in a hood. In the plant, engineering controls should be employed and 'good house-keeping' stressed to attain the objective of avoiding all possible exposure to benzene. The concentration of benzene vapor in the air should be checked regularly in work locations where the possibility of excessive exposure may be encountered. The con-

concentration of benzene in the plant atmosphere should not be permitted to exceed the threshold limit (25 p.p.m.). Respiratory equipment should be provided for all workers who might have exposure to concentrations of benzene in excess of the threshold limit.

Urine samples should be taken for biochemical analysis as a further check on the efficacy of the industrial hygiene methods and also to detect carelessness on the part of the individual worker.

B) Detection

(1) *Biochemical tests:* The urinary sulfate ratio, inorganic total (I/T) has been used for a number of years as an index of exposure to benzene. Eighty to ninety percent of the sulfate in normal urine is immediately precipitated by addition of barium ion since it is present in ionic form as inorganic sulfate (I). Ten to twenty per cent of the urinary sulfate is normally present in the form of ethereal sulfate, conjugated with phenols, indoles or cresols. The ethereal sulfates are readily hydrolyzed to inorganic sulfate and phenolic compounds by heating acidified urine. The sulfate precipitated by barium ion in the hydrolyzed urine specimen is designated as total sulfate (T). The quantity of ethereal sulfate is the difference between the amount of sulfate precipitated by barium ion in a hydrolyzed (T) and in an unhydrolyzed (I) urine aliquot. Exposure to benzene results in an increased urinary output of phenol sulfate (ethereal sulfate) and decrease in the quantity of inorganic sulfate. These changes lower the index, I/T . The value of the index in men exposed for hours to various atmospheric concentrations of benzene, and its interpretation in terms of health hazard are shown in Table 27.

Because the benzene is rapidly eliminated from the blood the urinary sulfate ratio returns to normal a few hours after exposure to benzene has ceased. For this reason, urine samples should be taken at the end of, or during the exposure period but not later than 2 hours after the termination of the exposure to

TABLE 27
RELATIONSHIP OF BENZENE VAPOR CONCENTRATION,
URINARY SULFATE RATIO, AND POTENTIAL HEALTH HAZARD*
(8-hour exposure)

<i>Benzene concentration (p.p.m.)</i>	<i>Urinary sulfate ratio (%)</i>	<i>Interpretation</i>
Nil	86	Normal
0-40	72	Hazardous
40-75	61	Hazardous
75-100	43	Hazardous
100-200	38	Very hazardous

* After Elkins, H. (1959).

benzene. Elkins (1959) found a marked difference in the urinary sulfate ratio of specimens taken in the morning and in the afternoon in workers exposed for 7-8 hours to benzene ranging concentration from 45-100 p.p.m. Urine specimens collected hours after exposure to benzene are of little value.

A decreased urinary sulfate ratio is not to be interpreted indicating the existence of clinical or biochemical injury. It is simply a test which shows that benzene has been absorbed in sufficient quantity to be excreted as phenol sulfate which alters the normal urinary sulfate ratio. Since benzene is metabolized by the liver the test may be unreliable in an individual with hepatic disease or malfunction of the liver.

The ethereal sulfates normally found in the urine are derived from phenol-forming amino acids, tyrosine, phenylalanine and tryptophan and other precursors in foods, such as coffee, bananas, smoked meats and fish. An excessive intake of these foods will alter the urinary sulfate ratio. Drugs which are phenolic compounds or capable of *in vivo* conversion to aromatic hydroxyl derivatives will also decrease the ratio of inorganic to total urinary sulfate.

The diurnal variation in urinary inorganic and total sulfate in an unexposed man is shown in Fig. 47.

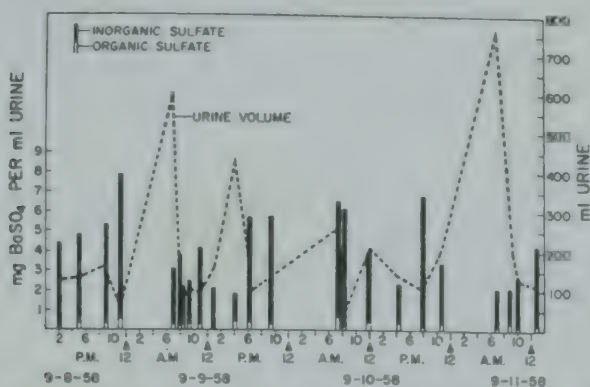


Fig. 47. Normal diurnal variation in urinary inorganic and ethereal sulphate in an unexposed man. (Gerarde, H. W., unpublished data).

Teisinger and Bergerová-Fišerová (1955) have used the 24-hour urinary phenol output as a test for exposure to benzene. Urinary phenol excretion exceeding 20 mg per liter is regarded as excessive and indicative of slight exposure to benzene; 10 mg of phenol per liter is interpreted as indicating exposure to less than 30 p.p.m. of benzene in the atmosphere during an 8-hour work day. A concentration of 100 mg of phenol per liter of urine was found to correlate with an 8-hour exposure to 30 p.p.m. of benzene in the air.

The presence of benzene in the blood or urine is direct evidence that an individual has had exposure to benzene. According to Teisinger a concentration of 50 μ g of benzene per liter of urine indicates slight exposure; 4000 μ g per liter signifies severe exposure to benzene.

(2) *Periodic health examination:* The frequency of the periodic physical examination of workers handling benzene depends on the adequacy of the engineering controls and the results of biochemical tests for exposure to benzene. If the threshold limit is not exceeded in the plant atmosphere and the biochemical tests for exposure are negative there is no need to conduct a periodic physical examination more often than once a year.

unless a more frequent examination is mandatory by law (see Chapter 6, p. 90).

The examination should include a brief interval history and physical examination together with a complete blood study. The following blood abnormalities are suggestive of possible exposure to benzene:

1. Leukocyte count below $4,000/\text{mm}^3$.
2. Erythrocyte count below $4,000,000/\text{mm}^3$.
3. Hemoglobin less than 12 grams/100 ml.
4. Platelets less than $100,000/\text{mm}^3$.
5. Differential count
 - a. Less than 50% polymorphonuclear leukocytes.
 - b. Increase in relative numbers of immature erythrocytes.

These deviations from normal warrant investigation of the worker's environment and detailed inquiry about other possible sources of exposure to benzene. The blood examination should be repeated at weekly intervals and unless there is noticeable improvement the worker should be withdrawn from further exposures.

(C) Treatment

The victim of acute benzene intoxication should be removed at once from the contaminated atmosphere. Artificial respiration should be started immediately if breathing has stopped. Oxygen should be administered as long as it is required to maintain the normal color of the skin. If oxygenation of the blood is maintained there is no need for stimulants. Epinephrine is contraindicated (see Chapter 6, p. 91). The victim should be kept warm, quiet and in a recumbent position.

Treatment for chronic benzene intoxication is supportive and symptomatic. Blood transfusions are indicated for anemia and antibiotics to prevent infection if the leukocyte count is markedly decreased. These are temporary measures used to prolong the life of the patient in the hope that the hemopoietic tissue will return to its normal state of cellular activity.

Mono-alkyl derivatives of benzene

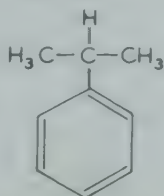
CUMENE

Synonyms

Isopropylbenzene, isopropylbenzol, 2-phenylpropane, cumol.

Molecular formula: C_9H_{12} .

Structural formula:



Molecular weight: 120.19.

Physical properties

A clear, colorless liquid with a sharp aromatic odor (see other table on pp. 110 and 111).

Sources, uses and probable modes of contact

Cumene is produced commercially by alkylation of benzene with propylene and by fractionation of petroleum distillates. During World War II it was produced in large quantities as a high octane blending component for use in aviation gasoline. Cumene was found to give excellent rich mixture performance in reciprocating aircraft engines. Fuels deficient in aromatics could be improved to meet take-off requirements by the addition of a relatively little cumene. The availability of cumene was a

PHYSICAL PROPERTIES OF

	<i>Cumene</i>	<i>Dodecylbenzene</i>
Boiling point	152.4° C (306.3° F)	280-300° C (536-572° F)
Melting point	—96.03° C (—140.9° F)	—3.0° C
Vapor pressure	10 mm Hg at 38.33° C	9 mm Hg at 172-175° C
Vapor density (air = 1)	4.2	8.47
Density of saturated vapor-air mixture at 760 mm Hg (air = 1)	1.03 at 38° C	1.064 at 172° C
Per cent in saturated air, 760 mm Hg	1.32 at 38.3° C	1.18 at 172° C
Liquid density at 25°/4°	0.85748	0.8708
Index of refraction	1.48874 at 25° C	1.4897 at 20° C
Solubility	Very limited in water. Sol. in ethanol, ether.	Insol. in water. Sol. in arom. hydrocarbons, ether, and chloroform.
Flash point	102° F (T.C.C.)	270° F (C.C.)
Flammable limits (per cent by vol. in air)		
Conversion factors (25° C and 760 mm Hg)		
1 p.p.m. of vapor	0.00492 mg/l	~ 0.010 mg/l
1 mg/liter of vapor	203.5 p.p.m.	~ 99 p.p.m.

OCARBONS DISCUSSED IN CHAPTER 8

<i>Styrene</i>	<i>α-Methylstyrene</i>	<i>Styrene</i>	<i>Toluene</i>
145.2° C (293.4° F)	165.38° C (329.7° F)	145.2° C (293.4° F)	110.4° C (230.7° F)
—30.6° C (—23.1° F)	23.21° C (73.8° F)	—30.6° C (—23.1° F)	—94.5° C (—138.1° F)
6.45 mm Hg at 25° C	2.5 mm Hg at 25° C	6.45 mm Hg at 25° C	36.7 mm Hg at 30° C
3.6	4.08	3.6	3.2
1.02 at 15° C	1.01 at 25° C	1.02 at 15° C	1.09 at 26° C
0.57 at 15° C	0.33 at 25° C	0.57 at 15° C	3.94 at 26° C
0.9021	0.9062	0.9021	0.861
1.5428 at 25° C	1.5386 at 20° C	1.5428 at 25° C	1.489 at 24° C
0.31 g/100 ml water at 25° C.	Insol. in water.	0.31 g/100 ml water at 25° C.	0.082 g/100 ml water at 22° C.
Miscible with ethanol, ether.	Miscible with arom. hydrocarbons, ethanol, ether, acetone.	Miscible with ethanol, ether.	Miscible with ethanol, ether, chloroform, glacial acetic acid, carbon disulfide.
86° F (T.C.C.)	136° F (C.C.)	86° F (T.C.C.)	40° F (C.C.)
1.10-6.10	0.90 (lower limit)	1.10-6.10	1.72-6.75
0.00426 mg/l 235.5 p.p.m.	0.00483 mg/l 207 p.p.m.	0.00426 mg/l 235.5 p.p.m.	0.00376 mg/l 266 p.p.m.

critical factor in the defense of Britain during World War II.

Cumene has recently become an important source of phenol and acetone. It is also a constituent of commercial aromatic petroleum solvents boiling in the range of 150 to 160°. The solvents are extensively used as thinners for paints and enamels.

The most likely modes of contact with cumene in its present industrial uses are by inhalation of vapors and mists, and skin contact with the liquid hydrocarbon.

Analytical methods

Cumene vapors in the air can be measured with field equipment suitable for the quantitative analysis of aromatic hydrocarbons described in Chapter 3. In the absence of interfering substances (aromatic hydrocarbons) cumene can be determined colorimetrically by nitration or by treatment with sulfuric acid-formaldehyde mixture. Cumene in blood and animal tissues has been determined by nitration after a preliminary separation of the hydrocarbon from the tissues by distillation (Fabre, *et al.*, 1955a). An ultra-violet spectro-photometric method for the determination of alkyl derivatives of benzene in blood may also be used for cumene (Guertin, D. and Gerarde, H. W., 1955).

Toxicology

Acute toxicity

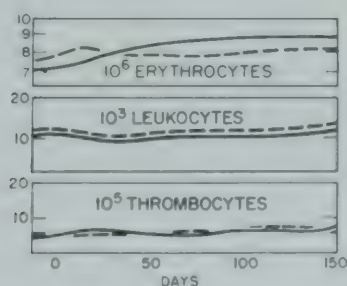
Liquid cumene is a primary skin irritant. It is absorbed slowly through the intact skin so that systemic intoxication resulting from the percutaneous absorption of cumene is highly improbable. Conjunctival irritation and lacrimation will result from direct contact of liquid cumene with the eye.

Direct contact of liquid cumene with pulmonary tissue (aspiration) will cause pulmonary edema and hemorrhage. The approximate oral LD-50 of cumene for male rats is 1.4 g/kg of body weight. The minimum lethal concentration (LC-50) of cumene vapors for mice is 2000 p.p.m. (10 mg/l) for a single 7-hour exposure. For purposes of comparison, the LC-50 value

or mice exposed to toluene and benzene vapors for 7 hours are 5000 p.p.m. and 10,000 p.p.m. respectively. On the basis of these values, cumene vapors are twice as toxic as the vapors of toluene, and 5 times as toxic as benzene vapors for a single exposure of 7 hours duration for the mouse. The effects observed in mice exposed to cumene vapors are: dilatation of cutaneous blood vessels, central nervous system depression varying from slight incoordination to narcosis, and depression of respiration (Werner, H. W. *et al.*, 1944). Cumene narcosis develops more slowly and lasts longer than the narcosis produced by benzene and toluene. The non-specific histopathological changes (congestion and fat accumulation) found in the liver and kidneys are commonly found after exposure to a number of solvent type chemicals (esters, ketones, ethers).

Chronic toxicity

Prolonged or repeated contact of liquid cumene with the skin may cause dermatitis due to the dehydrating and defatting action of the hydrocarbon on the skin. Wolf *et al.* (1956) dosed female rats 139 times by gastric intubation with 154 mg of cumene per kilogram of body weight without finding evidence of injury. The duration of the experiment was 194 days. An increase in kidney weight was observed when the dose was increased to 2 mg/kg; the number of doses and the duration of the experiment



48. Effect of inhalation of isopropylbenzene (cumene) vapor on peripheral blood in the rat, (2.5 mg/l, 8h/d and 6d/wk). — Isopropylbenzene. - - - Control. (Fabre, R. and Truhaut, R., 1955a).

riment were kept constant (139 doses in 194 days). The total femoral marrow cell population was not diminished in rats dose subcutaneously with 1 ml of cumene per kilogram of body weight daily for two weeks (Gerarde, H. W., 1956).

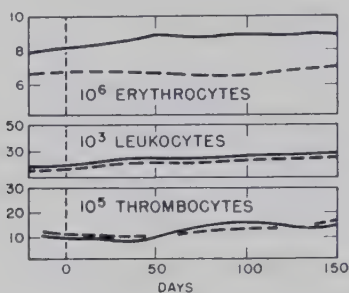


Fig. 49. Effect of inhalation of isopropylbenzene (cumene) vapor on peripheral blood in the rabbit. (2.5 mg/l, 8h/d and 6d/wk). — = Isopropylbenzene. - - - = Control. (Fabre, R. and Truhaut, R., 1955a)

Fabre *et al.* (1955a) have conducted the most extensive study on the chronic vapor inhalation toxicity of cumene. Rats and rabbits exposed to approximately 500 p.p.m. (2.5 mg/l) of cumene vapor 8 hours per day, 6 days per week for 150 days developed no significant deviations from normal in the peripheral blood (Fig. 48-49). The myelogram of the cumene dose rats was also normal. Hyperemia and congestion were found in the lungs, liver and kidneys of the animals exposed repeatedly to cumene vapors.

Biochemistry

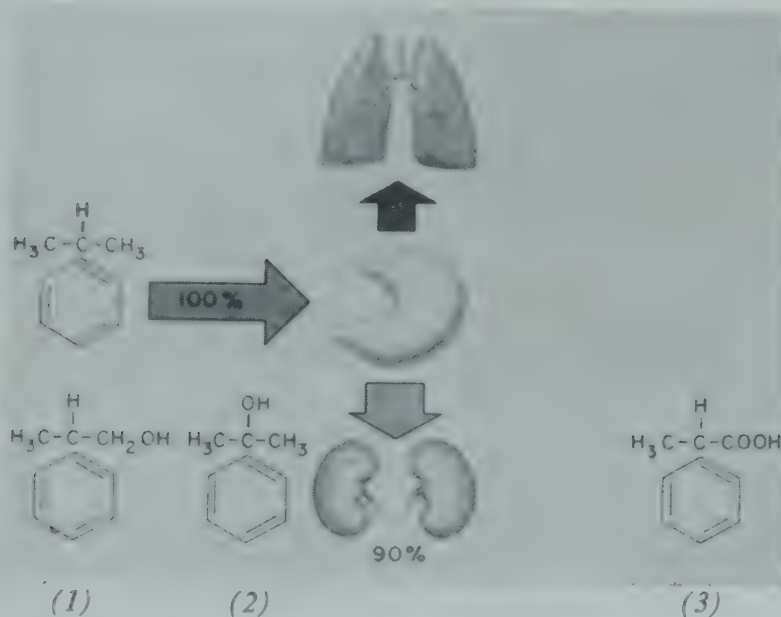
Cumene is absorbed into the blood by inhalation of the hydrocarbon vapor or mist; liquid cumene is absorbed from the gastrointestinal tract and slowly through the intact skin. According to Vallette and Cavier (1954), cumene is absorbed through the intact skin more rapidly than toluene, xylene or ethylbenzene (see Fig. 28, p. 46). A small fraction of the cumene absorbed into the blood is exhaled unchanged; the major portion is metabolized in the liver and excreted in the urine as water-soluble

TABLE 28

CONCENTRATION OF CUMENE IN BLOOD AND TISSUES OF THE RAT
AFTER REPEATED VAPOR EXPOSURE*
(2.5 mg/l, 8 h/day, 2 months)

Tissue	$\mu\text{g cumene/gram tissue (p.p.m.)}$	
	24 h after last exposure	48 h after last exposure
Blood	29	29
Brain	10	10
Cerebellum	53	20-30
Liver	7.5	8
Heart	> 5	> 5
Spleen	10	> 5
Bone marrow	—	> 5
Uterus	> 5	—

After Fabre, R. *et al.* (1955a).



50. Elimination and biotransformation of isopropylbenzene (cumene) in the rabbit in the 72-hour interval after a single oral dose. Principal urinary metabolites are left to right: (1) 2-Phenylpropan-1-ol, (2) 2-Phenylpropan-2-ol, (3) 2-Phenylpropanoic acid. (1) and (2) are conjugated with glucuronic acid, (3) with glycine. (Robinson, D. *et al.*, 1955).

metabolites. Table 28 shows the concentrations of cumene in the tissues of rats exposed repeatedly to vapors of the hydrocarbon. Cumene appears to be retained in the blood, brain and liver longer than in other tissues, such as the cerebellum and spleen. Eight p.p.m. of cumene was found in the blood of a rabbit 10 days after the 150th exposure to approximately 1300 p.p.m. (6.5 mg/l) of the hydrocarbon vapors. Cumene is eliminated from the blood and tissues more rapidly by the rabbit than the rat. This may explain the greater tolerance of the rabbit for cumene vapors.

The biotransformations of cumene in the rabbit are summarized in Fig. 50.

Threshold limit

The threshold limit for cumene has not been established. Based on the toxicological studies conducted with cumene and the acceptable limits established for toluene, ethylbenzene and the xylenes, the threshold limit for cumene probably should be in the range of 50-100 p.p.m.

Prevention, detection and treatment of exposure

(A) Prevention

Exposure to cumene vapors or aerosols and the liquid hydrocarbon should be kept to a minimum by care in handling on the part of the individual worker and in the plant by use of 'good housekeeping'.

Engineering controls should be used in the plant to maintain the air concentration at approximately 50 p.p.m. When excessive concentrations are unavoidably encountered in the case of accidental spills and in cleaning of tank cars or storage tanks, air masks and protective clothing should be used. Gloves impervious to cumene should be worn if it is impossible because of the nature of the work to avoid contact with the liquid hydrocarbon. Clothing that has become contaminated with cumene should be removed promptly and not be re-worn until laundered.

3) *Detection*

Since there is no established biochemical test for detecting exposure to cumene or for latent toxicity due to excessive absorption of the hydrocarbon, reliance must be placed on industrial hygiene methods to keep exposure to a minimum and, as further precaution on periodic health examinations of the workers. A periodic medical evaluation at approximately annual intervals should provide an adequate check on the efficacy of the preventive measures in keeping exposure to cumene at a safe level. According to Italian law, workers exposed to cumene and other aromatic hydrocarbons (see p. 90) must be examined at least semi-annually.

The health examination should include a brief interval history, physical examination and if considered desirable complete blood count. Particular attention should be directed in the medical history and physical examination to symptoms and signs of irritation of the skin, mucous membranes and the eyes.

4) *Treatment*

A person overcome by inhalation of cumene vapor should be removed immediately from the contaminated working area. Artificial respiration must be started at once if the victim has stopped breathing. Oxygen may be administered to maintain the normal color of the skin and mucous membranes. The use of stimulants is not necessary if breathing and oxygenation are normal. Epinephrine is contraindicated in case of collapse due to acute hydrocarbon intoxication. See Chapter 6, p. 91 for further details for the management of acute aromatic hydrocarbon vapor intoxication.

Chronic over-exposure to cumene may cause signs and symptoms of irritation of the eyes, mucous membranes and possibly the skin. These effects of chronic cumene intoxication respond favorably to discontinuation of the exposure in a normal individual.

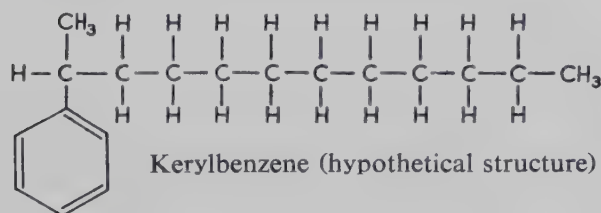
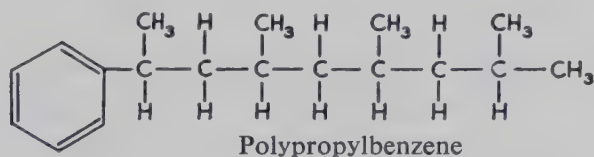
DODECYLBENZENE

Synonyms

Detergent alkylate, tetrapropylene benzene, phenyldodecan, polypropylbenzene, kerylbenzene.

Molecular formula: $C_{18}H_{30}$.

Structural formula:



Molecular weight: Av. 246.42.

Physical properties

A colorless, odorless liquid (see further table on pp. 110 and 111).

Sources, uses and probable modes of contact

The first commercial detergent alkylate was prepared by chlorinating a *narrow kerosine cut* and alkylating benzene with the resulting 'keryl chloride'. Distillation of the product gave a 'kerylbenzene' (hypothetical formula shown above). In 'kerylbenzene' the phenyl group occupies random positions along the chain.

Shortly after World War II a new type of alkylbenzene was introduced based on propylene polymer, primarily a tetrapropylene. After fractionation to the proper boiling ranges, it is reacted with benzene using HF , $AlCl_3$ or sulfuric acid catalyst. The alkylated product is the so-called 'dodecylbenzene' or detergent alkylate of commerce.

Detergent alkylate is converted into a wetting agent and detergent by reacting with sulfuric acid and then neutralizing. The sulfuric acid reaction product is normally treated with caustic soda to form sodium dodecylbenzene sulfonate which is the main ingredient in most synthetic detergents in the United States and the United Kingdom.

The most likely mode of contact with detergent alkylate in industrial applications is skin contact with the liquid and possibly with mists or aerosols of the hydrocarbon which might be inhaled.

Analytical methods

Although chemically detergent alkylate is relatively inert, the benzene ring undergoes most of the chemical reactions which form the basis for the quantitative and qualitative analysis of the alkyl derivatives of benzene. See Chapter 3 for discussion of general methods of analysis for the alkyl derivatives of benzene.

Toxicology

The acute oral toxicity of dodecylbenzene is greater than 5 ml/g of body weight for the male albino rat (Gerarde, H. W., 1959). There were no deaths in a group of 10 rats weighing approximately 225 grams which were dosed by stomach tube with 2.5 ml of a 1:1 v/v mixture of dodecylbenzene in olive oil. The animals showed no evidence of central nervous system involvement or other signs of systemic intoxication.

The direct aspiration of dodecylbenzene or a commercial detergent alkylate into the lungs of rats caused chemical pneumonitis, pulmonary hemorrhage and death. This is a general response of pulmonary tissue to hydrocarbons. A bland, non-irritating hydrocarbon such as *n*-octadecane or *n*-hexadecane causes a similar reaction when aspirated directly into the lung. Because of the low surface tension of the hydrocarbons, a small volume of the chemical spreads over a large organ surface and causes extensive tissue injury (Gerarde, H. W., 1959a).

The prolonged or repeated contact of detergent alkylate with the skin may cause dermatitis due to drying and removal of the natural fats from the cutaneous tissues.

There have been no studies reported in the literature on the effects of inhaling detergent alkylate vapors or mists. Based on analogy with similar hydrocarbons one would expect local irritation of the mucous membranes of the nose, throat and eyes after prolonged exposure to relatively high atmospheric concentrations of dodecylbenzene.

The lack of published information on the toxicity of detergent alkylate is probably due to the low order of toxicity and slight hazard inherent in the relatively large hydrocarbon molecule.

Biochemistry

There are no published reports on the biochemistry of detergent alkylate.

Dodecylbenzene administered to rats subcutaneously did not increase the urinary output of ethereal sulfate. (See Table 2, p. 74). This observation indicates that the benzene ring is not hydroxylated in the metabolism of dodecylbenzene. Based on the metabolic studies described with *n*-alkyl benzenes (Chapter 4) the dodecylbenzene side chain is probably oxidized to alcohol and carboxylic acid derivatives. These metabolites are then excreted in the urine conjugated with glycine and glucuronic acid.

The metabolism of the sulfonated detergent alkylate by microorganisms has been studied extensively since the introduction of the detergent for household use. The objective of these studies is to find an explanation for the excessive foaming and frothing in sewage disposal plants. Metabolic studies with microorganisms have shown that the terminal methyl group of the alkyl benzene sulfonate is oxidized to carboxyl. Complete degradation of the molecule occurs when the benzene is attached to a primary or secondary carbon atom of the alkyl group. Tertiary alkyl benzene sulfonates are not completely degraded by bacteria presumably because biological oxidation is blocked.

the tertiary carbon atom. This blocking effect of the branched side-chain on the bio-oxidation of the alkyl derivatives of benzene is also known to exist in mammalian systems (see Chapter 4).

Threshold limit

The maximum allowable concentration (MAC) for dodecylbenzene (detergent alkylate) in the working atmosphere for an eight-hour work day has not been established due to inadequate toxicological information. A concentration of 200 p.p.m. appears to be a reasonable figure.

Prevention, detection and treatment of exposure

Prevention

Detergent alkylate has a low order of mammalian toxicity and should present little hazard in normal handling because of its low vapor pressure at room temperature. Nevertheless, inhalation of vapors or mists containing the hydrocarbon, and skin contact with the liquid should be kept to a minimum. This can be accomplished on the part of the individual worker by care in handling dodecylbenzene. In the plant using large quantities of dodecylbenzene, engineering controls should be employed to maintain the air concentration at a level which is safe for repeated daily exposure. Workers unavoidably exposed to excessive vapor concentrations or having direct skin contact with the liquid hydrocarbon should be provided with suitable respiratory equipment, protective garments and gloves, and goggles to protect the eyes.

Detection

There is no clinical test for detecting exposure to dodecylbenzene or latent systemic intoxication resulting from excessive absorption of the hydrocarbon. The detection and estimation of microgram quantities of the metabolites of dodecylbenzene in the hydrocarbon could form the basis of a test for exposure to dodecylbenzene.

Periodic health examinations should be conducted at regular intervals on workers exposed to dodecylbenzene. The interval between medical history and physical examination should be directed particularly to eliciting and detecting evidence of eye, mucous membrane and skin irritation.

(C) Treatment

It is highly improbable that the vapor concentration of dodecylbenzene could attain a sufficient concentration in the air to cause acute intoxication by inhalation of hydrocarbon vapor except under unusual circumstances, such as working in a confined space with poor ventilation or the circumstance of a large accidental spill of liquid at an elevated temperature. In the event of acute poisoning by dodecylbenzene vapor the first aid treatment and medical management are the same as described for acute intoxication due to the more volatile aromatic hydrocarbons (see Chapter 6, p. 90).

Chronic dodecylbenzene intoxication consisting of eye, mucous membrane irritation and dermatitis responds favorably to removal of the individual from further exposure.

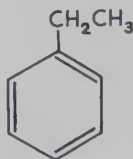
ETHYLBENZENE

Synonyms

Phenylethane, ethylbenzol.

Molecular formula: C_8H_{10} .

Structural formula:



Molecular weight: 106.16.

Physical properties

A clear, colorless liquid with an aromatic odor (see further table on pp. 110 and 111).

sources, uses and probable modes of contact

Ethylbenzene is manufactured commercially by dehydrogenation of cycloparaffins, alkylation of benzene, cyclization and aromatization of paraffin precursors, and by direct recovery from a mixed xylene stream by ultrafractionation.

It is used principally as a source of styrene (vinylbenzene) but also a constituent of commercial aromatic solvent mixtures and of automotive and aviation gasoline.

The most likely modes of contact with ethylbenzene in its present commercial use are by inhalation of vapors and mists and skin contact with the liquid hydrocarbon.

analytical methods

The concentration of ethylbenzene in air can be determined with direct-reading field equipment and by the general chemical and physical methods of analysis for the alkyl derivatives of benzene described in Chapter 3.

The concentration of ethylbenzene in biological samples (issues, blood and urine) can be determined by separating the hydrocarbon from the sample by extraction and/or distillation and subsequent analysis by colorimetric or spectrophotometric procedures. An ultraviolet spectrophotometric method has been recently described for the determination of ethylbenzene in blood (Guertin, D., and Gerarde, H. W., 1959).

toxicology

acute toxicity

Liquid ethylbenzene is a primary skin irritant which may cause erythema and blistering of the skin if contact is prolonged. The aspiration of liquid ethylbenzene into the lungs will cause chemical pneumonitis characterized by pulmonary edema and hemorrhage. Since ethylbenzene has a low viscosity and low surface tension, a small volume of liquid will spread over a large surface of pulmonary tissue and consequently extensive injury may result from the aspiration of a small volume of the

liquid hydrocarbon (see Chapter 4, p. 43). Ethylbenzene splashed into the eye may cause corneal injury if the liquid is not promptly removed by flooding the eye with water. The approximate oral LD-50 of ethylbenzene for rats is 3.5 g/kg of body weight (Wolf M. A. *et al.*, 1956).

The odor of ethylbenzene vapors can be detected in the air at a concentration of a few parts per million. A concentration of 1000 p.p.m. (0.1 %) is very irritating to the eyes at the moment of exposure, but as the exposure is prolonged a tolerance develops and the intensity of the eye irritation diminishes. Men exposed to 2000 p.p.m. (0.2 %) experienced immediate, severe eye irritation, lacrimation, and irritation of the mucous membranes of the nose. After 6 minutes of exposure to this atmosphere dizziness became apparent in the subjects although the irritation of the mucous membranes decreased. An atmosphere containing 5000 p.p.m. (0.5 %) of ethylbenzene caused an intolerable irritation of the eyes and mucous membranes of the

TABLE 29
HUMAN RESPONSE TO ETHYLBENZENE VAPORS*

Concentration mg/l	p.p.m.	Exposure time	Response
21.75	5000	Few seconds	Intolerable irritation of nose, eyes and throat.
8.7	2000	Few seconds	Severe eye, nose and mucous membrane irritation. Lacrimation.
8.7	2000	6 minutes	Central nervous system effects. Dizziness.
4.35	1000	Few seconds	Eye irritation.
4.35	1000	Minutes	Eye irritation diminishes.
0.87	200	Threshold limit**	
0.043	> 10	Few seconds	Odor detectable

* After Yant, W. P. *et al.*, 1930.

** American Conference of Governmental Industrial Hygienists, 1959.

dose (Yant, W. P. *et al.*, 1930). The effects of ethylbenzene vapor on man are shown in Table 29.

The acute effects of ethylbenzene vapors on guinea pigs, according to Yant *et al.* (1930), are summarized in Table 30.

TABLE 30
TOXICITY OF ETHYLBENZENE VAPOR
(Guinea pig)*

Concentration (p.p.m.)	Response
10,000	Fatal in a few minutes.
5,000	Dangerous to life in 30 to 60 minutes.
3,000	Maximum 1 hour exposure without serious symptoms.
1,000	Maximum exposure for several hours without serious disturbance.

After Yant, W. P., *et al.* (1930).

Animals that died from exposure had generalized visceral hyperemia and intense congestion and edema of the lungs.

Chronic toxicity

Repeated or prolonged contact of liquid ethylbenzene with the skin may cause dermatitis due to the defatting action of the hydrocarbon. Systemic toxicity from the percutaneous absorption of ethylbenzene through the intact skin is highly improbable. Repeated application of ethylbenzene to the intact skin of rabbits indicated that the hydrocarbon was not absorbed in sufficient quantity to cause acute systemic effects (Wolf, M. *et al.*, 1956).

The most extensive study on the chronic toxicity of ethylbenzene vapor has been reported by Wolf *et al.* (1956) with rats, rabbits, guinea pigs, and monkeys. These animals were exposed to concentrations of ethylbenzene ranging from 400 p.p.m. to 2200 p.p.m., 7 to 8 hours per day, 5 days a week for

as long as 6 months. A slight increase in the average weights of the kidneys and livers was found in the rats exposed to 400 p.p.m. for 186 days. The guinea pigs, rabbits and monkeys showed no evidence of adverse effects from these exposures. Hematological studies were conducted in addition to the usual criteria of injury used in toxicological studies with animals. Rats injected subcutaneously with 1.0 ml of ethylbenzene per kg of body weight daily for two weeks had a normal total femoral marrow nucleated cell count. These animals developed a leukocytosis in contrast with the severe leukopenias found in benzene-dosed rats which served as the positive controls (Gerarde, H. W., 1956). Repeated oral feeding of ethylbenzene to female rats (130 doses of 136 mg/kg) produced no demonstrable injury (Wolf, M. *et al.*, 1956).

Biochemistry

Ethylbenzene vapors and mists are absorbed into the blood by inhalation. Liquid ethylbenzene is absorbed from the gastrointestinal tract and much more slowly through the intact skin. A peak concentration of 15 p.p.m. was found in the blood of rats six hours after subcutaneous dosing with 2.5 ml of a 1:1 mixture in olive oil (see Fig. 37, p. 67). A small proportion of the ethylbenzene that is absorbed into the blood is exhaled unchanged. The principal metabolites of ethylbenzene in the rabbit are hippuric acid and methylphenylcarbinol glucosiduronic acid. These two end-products are produced in approximately equal amounts accounting for 60–70% of the dose given orally. The minor metabolites of ethylbenzene are mandelic acid (2%) and phenaceturic acid (10–20%). The biotransformations of ethylbenzene in the rabbit are summarized in Fig. 51.

Threshold limit

The threshold limit established for ethylbenzene for an 8-hour work day is 200 p.p.m. (American Conference of Governmental Industrial Hygienists, 1959).

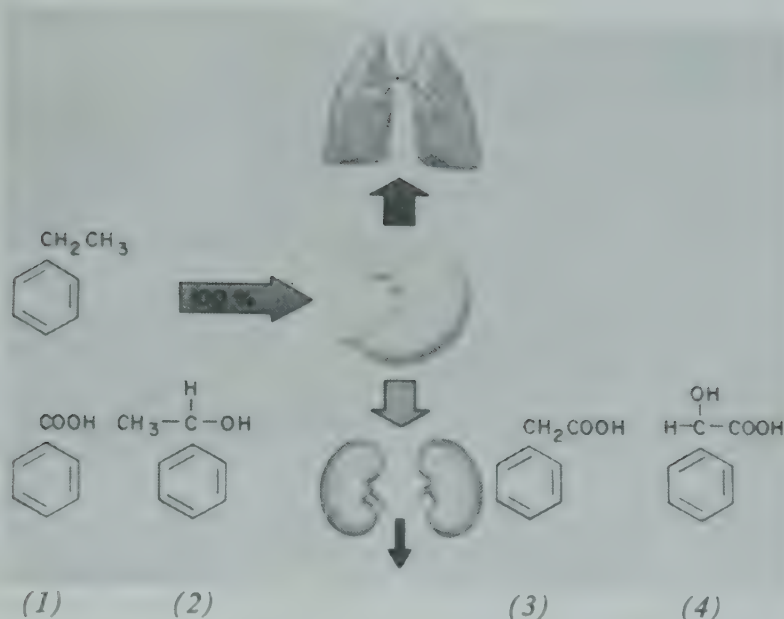


Fig. 51. Elimination and biotransformation of ethylbenzene in the rabbit in the 72-hour interval after a single oral dose. Principal urinary metabolites are left to right: (1) Benzoic acid, (2) Methylphenyl-carbinol, (3) Phenylacetic acid and (4) Mandelic acid. (1), (3) and (4) are conjugated with glycine, (2) with glucuronic acid. (El Masri, A. M. *et al.*, 1956).

Prevention, detection and treatment of exposure

(A) Prevention

Exposure to ethylbenzene vapors or mists and the liquid hydrocarbon should be kept to a minimum by care in handling on the part of the individual worker. In the plant, engineering controls and industrial hygiene methods and practices should be employed to attain the same objective.

Adequate ventilation should be provided at all times. Workers should wear protective gloves to prevent exposure of the skin under circumstances in which contact with the hydrocarbon is apt to occur. Respiratory equipment should be provided for all workers who must undergo exposure to concentrations of ethylbenzene in excess of 400 p.p.m. for more than a few minutes.

(B) Detection

There is no established clinical test or biochemical test for the detection of latent toxicity due to excessive absorption of ethylbenzene. Since hippuric acid is one of the principal metabolites of ethylbenzene, this may serve as a test for exposure to ethylbenzene in the absence of exposure to toluene, styrene, or other hippuric acid precursors. The relationship between ethylbenzene air concentration, exposure time and urinary hippuric acid output for man has not been established (see Toluene, p. 148). At the present time, reliance must be placed on industrial hygiene methods to keep exposure to ethylbenzene to a minimum. Periodic health examinations of employees should be provided as a further precaution. If the concentration of ethylbenzene vapor in the plant atmosphere does not exceed the threshold limit and 'good housekeeping' and careful handling prevail, there is no need to examine the workers oftener than once a year unless the law requires more frequent examination (see Chapter 1, p. 90).

The examination should include a brief interval history, physical examination and complete blood count. Particular attention should be directed in the medical history and physical examination to complaints or evidence of eye or mucous membrane irritation and dermatitis. The working environment should be investigated if the employee gives a history of chronic mucous membrane irritation or if evidence of skin and/or mucous membrane irritation is found on physical examination.

(C) Treatment

The victim of acute ethylbenzene vapor poisoning must be removed at once from the contaminated atmosphere. If breathing has stopped, artificial respiration should be started immediately. If oxygen is available it should be administered as long as it is necessary to maintain the normal color of the skin and mucous membranes. The victim should be kept quiet, warm and in a recumbent position. There is usually no need to use stimulants.

If the individual is breathing normally. Epinephrine is definitely contra-indicated for treatment of collapse due to acute hydrocarbon intoxication (see Chapter 6, p. 91).

The manifestations of chronic ethylbenzene intoxication may consist of signs of irritation of the eyes and mucous membranes, and dermatitis. In a normal individual withdrawal from further exposure results in spontaneous complete recovery.

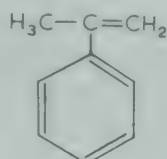
alpha-METHYLSTYRENE

Synonyms

Isopropenylbenzene, *beta*- or 2-phenylpropylene, *beta*- or 2-phenylpropene, *as*-methylphenylethylene.

Molecular formula: C_9H_{10} .

Structural formula:



Molecular weight: 118.17.

Physical properties

A colorless liquid having a sharp aromatic odor (see further data on pp. 110 and 111).

Sources, uses and probable modes of contact

alpha-Methylstyrene of high purity can be synthesized by alkylation of benzene with propylene using an HF or sulfuric acid catalyst.

It is used as a starting material for synthesis in the chemical and drug industry and is also polymerized to form plastics and acid resins.

In the present industrial applications of *alpha*-methylstyrene, the most likely modes of contact with this hydrocarbon are vapor inhalation and skin contact with the liquid.

Analytical methods

alpha-Methylstyrene undergoes all of the general reactions of the monocyclic aromatic hydrocarbons. It absorbs strongly in the ultraviolet, can be nitrated, and forms colored complexes with sulfuric acid-formaldehyde mixture. These general methods form the basis for the qualitative and quantitative analysis of the hydrocarbon in the air and biological fluids (see Chapter 1).

Toxicology

The most extensive toxicological studies on *alpha*-methylstyrene have been conducted by Wolf *et al.* (1956).

The results of limited odor and mucous membrane irritation studies on human subjects are summarized in Table 31. Table 32.

TABLE 31
HUMAN RESPONSE TO ALPHA-METHYLSTYRENE VAPOR*

Concentration (p.p.m.)	Response
600 or more	Very strong odor; strong eye and nasal irritation.
200	Strong objectionable odor.
100	Strong tolerable odor.
50	Odor detectable; no mucous membrane irritation.
> 10	Odor not detectable.

* After Wolf, M. A. *et al.* (1956).

subjects entered a sealed room containing known concentration of the hydrocarbon in the atmosphere and recorded their reactions with respect to odor, eye irritation and nasal irritation.

The direct instillation of the liquid hydrocarbon into the conjunctival sac of the rabbit's eye caused slight irritation of the conjunctival membrane but no corneal injury.

The repeated application of undiluted liquid *alpha*-methylstyrene to the ears and shaved abdominal skin of the rabbit caused erythema, edema, and exfoliation of the superficial layer.

of the skin. Although the liquid hydrocarbon was confined during topical application to the skin, it did not cause the blistering which was observed in rabbits dosed similarly with benzene, xylene, ethylbenzene and vinyltoluene. As judged by the gross appearance, behavior, and body-weight of the rabbits during the skin application tests, there was no indication that *alpha*-methylstyrene was absorbed in sufficient quantity to cause acute systemic intoxication.

The approximate oral LD-50 of *alpha*-methylstyrene for the male albino rat was found to be 4.9 g per kg of body weight. Post-mortem examination showed that these animals had slight liver abnormality and kidney involvement of questionable significance.

Rats, guinea pigs, rabbits and rhesus monkeys of both sexes were exposed repeatedly to vapors of the hydrocarbon for 7-8 hours per day, 5 days a week for up to 6 months. A considerable number of the rats and guinea pigs died after exposure to the highest concentration of 3000 p.p.m. (14.49 mg/l) of the hydrocarbon. The highest vapor concentration to which the rabbits and monkeys were exposed was 600 p.p.m. (2.90 mg/l). Some deaths were recorded in the group of rabbits exposed to this concentration after 152 exposures, but no ill effects were noted in a female monkey after 212 7-8 hour exposures. Growth depression and increase in liver and kidney weights were found in the rats and guinea pigs after 144 exposures to 600 p.p.m. 7-8 hours per day. No evidence of injury was found in any of the animals exposed to a concentration of 200 p.p.m. of *alpha*-methylstyrene for 139 7-8 hour exposure periods over an experimental interval of 197 days.

A most important negative finding in this excellent investigation was the absence of any evidence of injury to the blood-forming tissues.

Biochemistry

There is no information in the literature describing metabolic

studies conducted with *alpha*-methylstyrene. Based on current knowledge of the metabolism of mono-alkyl benzenes, it is highly probable that the metabolic transformations of *alpha*-methylstyrene occur principally on the side chain. This is supported by the observation that in rats dosed subcutaneously with this hydrocarbon, there was no significant change in the urinary excretion of ethereal sulfate (see Table 21 p. 74).

Threshold limit

The maximum allowable concentration (MAC) of *alpha*-methylstyrene in the atmosphere for an 8-hour workday has been set at 100 p.p.m. (American Conference of Governmental Industrial Hygienists, 1959).

Based on the results of toxicological studies on animals, together with the data on experiments on human subjects, it is probable that vapor concentrations of *alpha*-methylstyrene which will voluntarily be tolerated by most persons will not cause adverse systemic effects. The vapors of the hydrocarbon are definitely disagreeable at concentrations well below the levels capable of causing systemic injury. Wolf *et al.* suggest that a threshold limit of 200 p.p.m. would be appropriate. However, to insure freedom from complaints of disagreeable odor and mucous membrane irritation, the concentration of *alpha*-methylstyrene will probably have to be maintained below 100 p.p.m.

Prevention, detection and treatment of exposure

In general, the discussion presented in the section on prevention, detection and treatment of styrene exposure is applicable to *alpha*-methylstyrene, except for the suggestion that urinary hippuric acid may serve as a test for exposure. There is no information in the published literature regarding the chemical nature of the specific metabolites of *alpha*-methylstyrene in experimental animals or in man. It is highly probable that the metabolic conversions of the hydrocarbon involve alteration

of the alkyl side chain rather than hydroxylation of the ring. This is supported by the observation that the urinary sulfate ratio is essentially normal in rats dosed subcutaneously with *alpha*-methylstyrene (see Table 21, p. 74). The determination of the specific metabolites of *alpha*-methylstyrene in the urine may form the basis for a test of exposure to the hydrocarbon. The validity of the test as a practical index of exposure under actual working conditions requires correlative clinical studies of air concentrations of *alpha*-methylstyrene, exposure times and amounts of metabolite found in the urine. The foregoing discussion also applies to the possibility of using the urinary hydrocarbon concentration as a test for exposure to *alpha*-methylstyrene.

STYRENE

Synonyms

Vinylbenzene, phenylethylene, styrene monomer, phenethylene, phenylethylene, styrolene, cinnamene, cinnamenol, cinnamol.

Molecular formula: C_8H_8 .



Molecular weight: 104.14.

Physical properties

A clear, colorless liquid with a disagreeable odor (see further table on pp. 110 and 111).

Sources, uses and probable modes of contact

Styrene is produced commercially by the dehydrogenation of ethylbenzene. It can also be obtained from benzaldehyde and occurs naturally in the sap of styraceous trees.

Styrene is used extensively in the production of synthetic

rubber and resins (polystyrene plastic), as a starting material in the manufacture of emulsifying agents for distillates and oils and as an intermediate in chemical synthesis. It is also used as a modifier or solvent for many polyester resins.

The most likely mode of contact with styrene in industrial applications is by inhalation of vapors and mists, and skin contact with the liquid in the event of accidental spills or leaks in equipment.

Analytical methods

Rowe *et al.* (1943) have described methods for air sampling and analysis of styrene by ultraviolet and infrared absorption, and also by visual colorimetry based on nitration. The interferometer, combustible gas indicator and aromatic hydrocarbon detector may also be used for field testing after calibration of the apparatus for this hydrocarbon (see Chapter 3). Styrene can be determined in biological fluids and tissues by ultraviolet absorption, nitration or color formation with sulfuric acid formaldehyde mixture after separation of the hydrocarbon by extraction or distillation.

Toxicology

(A) Animal studies

Acute toxicity: Liquid styrene is a primary skin irritant which causes erythema and defatting of tissue on direct contact. If contact with liquid styrene is prolonged, blistering of the skin may result. The aspiration of liquid styrene into the lungs will cause chemical pneumonitis due to direct local injury at the site of contact with pulmonary tissue (see Chapter 4, p. 43). Liquid styrene and concentrated styrene vapors are extremely irritating to the eyes.

Laboratory animals exposed to concentrations of styrene in air ranging from 650 to 1300 p.p.m. show evidence of severe eye and nose irritation. Weakness, incoordination and unsteady gait, and signs of central nervous system involvement are observed.

ved in these animals when exposure to these concentrations (650 to 1300 p.p.m.) is prolonged from 12 to 30 hours. Animals tolerate 8 hours of continuous exposure to 1300 p.p.m. without developing any signs of central nervous system involvement. If the concentration is increased to 2500 p.p.m. local irritation of the mucous membranes and the eyes is more severe. At this concentration the signs of central nervous system depression also appear. A continuous exposure of 10 hours to 2500 p.p.m. produced unconsciousness and death. A one hour exposure to 5000 p.p.m. or a few minutes exposure to 10,000 p.p.m. of styrene vapor in air caused unconsciousness and fatalities in experimental animals (Rowe, V. K. *et al.*, 1943). The relationship between styrene vapor concentration and response in animals is shown in Table 32.

TABLE 32

RELATIONSHIP OF STYRENE VAPOR

CONCENTRATION AND EXPOSURE TIME TO RESPONSE IN ANIMALS*

Concentration p.p.m. mg/l		Exposure time	Response
650-1300	2.7-5.5	8 hours	Mucous membrane irritation (mice).
1300	5.5	12 hours	Weakness, incoordination, unsteady gait (rats, mice).
2400	10.2	8 hours	Weakness, stupor (rats).
2500	10.65	10 hours	Coma, death (rat).
5000	21.3	1 hour	Coma (rat).
10,000	42.6	minutes	Death (mice).

* After Rowe, V. K. *et al.* (1943).

The principal positive pathological findings in animals exposed to styrene vapor consisted of severe pulmonary irritation, congestion, edema, hemorrhage and leukocytic infiltration.

The oral LD-50 of styrene for the rat is 5.0 g/kg of body weight (Wolf, M. A. *et al.*, 1956).

Chronic toxicity: Rats and rabbits exposed to 1300 p.p.m. of styrene vapors in air, 7 to 8 hours per day, 5 days per week for 6 months showed evidence of local irritation to the mucous membranes of the respiratory tract and the eyes. There was no evidence of systemic intoxication in these animals. They gained weight at a normal rate and no deviations from normal were found in the peripheral blood. Guinea pigs appear to be more susceptible than rats and rabbits to injury produced by styrene vapors. Ten out of 100 guinea pigs exposed to 1300 p.p.m. of styrene vapor died from chemical pneumonitis after a few 7 to 8 hour exposures. Ninety animals of the original group of 100 survived 6 months of daily exposure to this concentration of styrene. Post-mortem examination of the tissues of these animals revealed no abnormality on gross or microscopic examination (Spencer, H. C. *et al.*, 1942).

(B) Human experience

Styrene vapor in concentrations of 200 to 400 p.p.m. has a transient irritating effect on the eyes and mucous membranes of the nose. Human subjects exposed to concentrations of approximately 500 p.p.m. complained of irritation of the eyes and throat which was accompanied by coughing in some individuals (Wolf, M. A., 1956). When the concentration of styrene is increased to 800 p.p.m. human subjects experience immediate eye and throat irritation on entry into this atmosphere. This is quickly followed by increased secretions from the nose and a metallic taste in the mouth. Signs of systemic intoxication in these men included: drowsiness, listlessness, muscular weakness and unsteadiness (Carpenter, C. P. *et al.*, 1944). The effects of styrene vapor in man are summarized in Table 33.

'Styrene-sickness' characterized by nausea, vomiting, loss of appetite and general weakness has been described in a group of employees working with styrene in plastic operations. The du-

TABLE 33
HUMAN RESPONSE TO STYRENE VAPOR*

Concentration (p.p.m.)	Response
800	Immediate eye and throat irritation; metallic taste; drowsiness, depression, weakness.
600	Strong odor; eye and nasal irritation.
400-200	Strong objectionable odor.
100	Strong tolerable odor.
60	Odor detectable; no mucous membrane irritation.
> 10	Odor not detectable.

*After Wolf, M. A. *et al.* (1956) and Carpenter, C. P. *et al.* (1944).

ation of these symptoms was only a few hours (Rogers, J. C., 1956). Repeated or prolonged skin contact with styrene may lead to the development of dermatitis (rough, dry and fissured skin) due to the removal of the natural oils in the tissue. According to Rogers (1957) fair-skinned individuals appear to be less resistant to the defatting and dehydrating actions of styrene than dark-skinned persons.

Biochemistry

Styrene is absorbed into the blood by inhalation of vapors or mists containing the hydrocarbon, from the gastrointestinal tract after oral administration of the liquid, and much more slowly by application of the liquid hydrocarbon to the intact skin. From 50 to 90% of the styrene administered orally to rabbits is eliminated as hippuric acid and mandelic acid in the urine. About 2% of the oral dose is exhaled as unchanged hydrocarbon. Styrene is exhaled unchanged through the lungs as long as the hydrocarbon is present in the blood stream. C-14 labeled styrene injected subcutaneously into rats is distributed almost all the tissues within an hour after dosing (Table 34). Practically all of the radioactivity was eliminated within 35

hours. A small fraction of the styrene injected subcutaneous in rats is exhaled unchanged through the lungs. The major portion is excreted as urinary metabolites. The elimination at

TABLE 34

DISTRIBUTION OF RADIOACTIVITY IN TISSUES AND EXCRETA OF RATS
INJECTED SUBCUTANEOUSLY WITH STYRENE- ^{14}C *

	<i>Per cent of dose</i>		
	<i>1 h</i>	<i>6 h</i>	<i>24 h</i>
Site of injection	47.20	28.05	2.9
Urine	4.02	37.20	71.5
Feces	0.00	0.41	2.9
Respiratory CO_2	0.00	6.02	11.5
Pancreas	0.32	0.08	0.9
Kidneys	1.82	0.48	0.9
Lungs	0.16	0.07	0.9
Stomach	0.27	0.06	0.9
Large intestine	0.35	0.19	0.9
Small intestine	0.49	0.26	0.9
Heart	0.15	0.09	0.9
Spleen	0.06	0.02	0.9
Liver	4.62	1.01	0.9
Adrenals	0.91	0.08	0.9
Blood	1.02	0.84	0.9
Bone	0.00	0.01	0.9
Brain	0.01	0.01	0.9
Thymus	0.01	0.00	0.9
Unchanged exhaled styrene	0.03	1.40	2.9

* After Danishefsky, I., and Willhite, M. (1954).

biotransformation of styrene in the rabbit and rat after dosing by the oral and subcutaneous routes of administration are shown in Figs. 52 and 53.

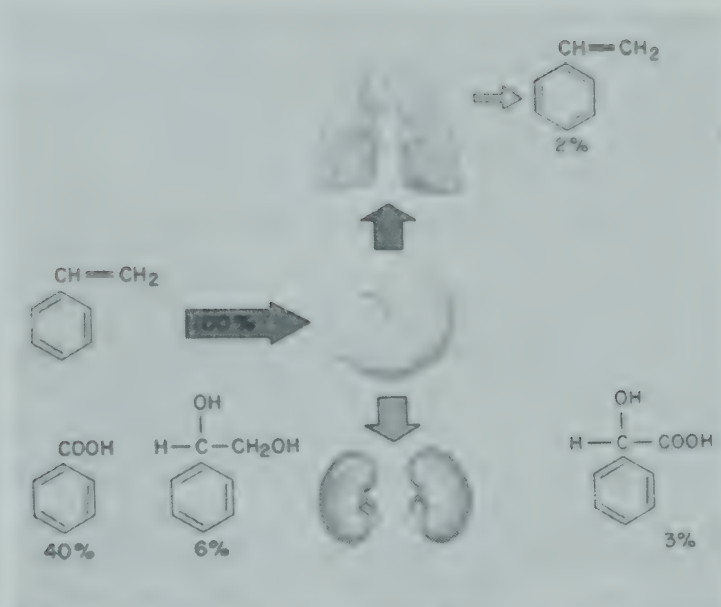


Fig. 52. Elimination and biotransformation of styrene in the rabbit in the 72-hour interval after a single oral dose. Principal urinary metabolites are, left to right: Benzoic acid (conjugated with glycine), Phenylglycol (conjugated with glucuronic acid) and mandelic acid. (El Masri, A.M. *et al.*, 1958).

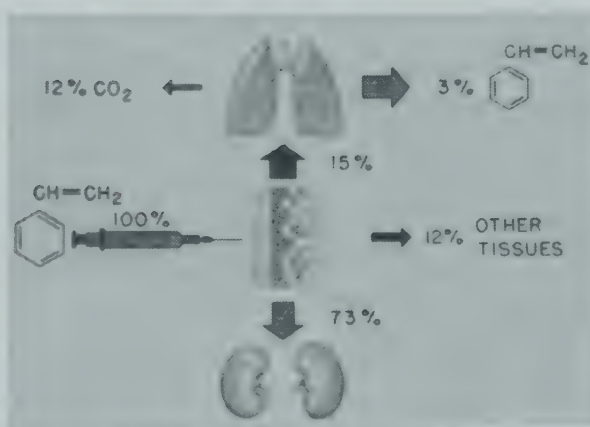


Fig. 53. The elimination of styrene after subcutaneous injection in the rat. Urinary metabolites are not isolated or positively identified.

(Danishefsky, I. and Willhite, M., 1954).

Threshold limit

The threshold limit for styrene has been set at 100 p.p.m. (approximately 420 mg/m³ of air) by the American Conference of Governmental Industrial Hygienists (1959).

Prevention, detection and treatment of exposure

(A) Prevention

The engineering control methods described for other volatile aromatic hydrocarbons (benzene, ethylbenzene, toluene) should be employed in the plant to maintain the atmospheric concentration of styrene at the threshold limit of 100 p.p.m. The individual worker, technician or chemist should avoid unnecessary inhalation of styrene vapors or skin contact with the liquid hydrocarbon. Persons who are unavoidably exposed to concentrations of styrene vapor in excess of the maximum allowable concentration should be properly protected with suitable respiratory equipment. Gloves impervious to styrene should be worn if contact with the hands cannot be avoided.

(B) Detection

There is no established test for exposure to styrene or biological chemical test for the detection of incipient toxicity due to the absorption of the hydrocarbon. The observation by Carpenter *et al.* (1944) that urinary hippuric acid is increased in man after exposure to styrene vapor suggests that hippuric acid output may be used as a test for exposure to the hydrocarbon. In order to prove the validity of this test a clinical study correlating atmospheric concentrations, exposure time and urinary hippuric acid excretion must be conducted. The test would not be specific for styrene exposure since toluene is also metabolized to hippuric acid in man. The urinary hippuric acid output has been used as a test for exposure to toluene under actual working conditions. See p. 148 for further discussion of the limitations of this test.

An annual periodic health examination should be conducted

workers who are exposed to styrene. This should include brief interval medical history, physical examination and complete blood count. The physician should pay particular attention to symptoms and signs of eye and mucous membrane irritation and dermatitis in taking the medical history and in the course of the physical examination.

Treatment

The first aid treatment and medical management of acute poisoning or intoxication due to volatile aromatic hydrocarbons is described in detail in Chapter 6, p. 91.

Chronic styrene intoxication, manifested by signs and symptoms of chronic eye, mucous membrane and skin irritation responds favorably to removal of the individual from further exposure to the hydrocarbon.

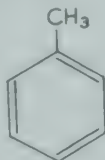
TOLUENE

Synonyms

Toluol, methylbenzene, phenylmethane, methylbenzol.

Molecular formula: C_7H_8 .

Structural formula:



Molecular weight: 92.13.

Physical properties

Clear, colorless, flammable liquid with an odor similar to benzene (see further table on pp. 110 and 111).

Preparation, uses and probable modes of contact

Toluene is a petrochemical and a by-product of the coke-oven industry. In the petroleum industry it is obtained by the hydrogenation of cycloparaffinic fractions or by cyclization and aromatization of saturated aliphatic hydrocarbons. From

coke-oven operations it is recovered from the gases and coal

Toluene is used extensively as a starting material for the synthesis of explosives and dyes in the chemical industry, as a thinner for paints, varnishes, enamels and lacquers, and as a solvent for gums, fats and resins. It is also a constituent of aviation and automotive fuels.

Because of its high vapor pressure at room temperature, the most probable mode of contact in individuals working with toluene is by vapor inhalation. Skin contact may also occur, particularly following accidental spillage and leaks and breathing in equipment containing toluene.

Methods of analysis

The concentration of toluene in air can be determined by direct reading field equipment and by the general laboratory procedures described in Chapter 3. Maffett *et al.* (1956) have described a rapid direct procedure for the collection and determination of micro quantities of toluene vapor in air.

Colorimetric chemical methods based on nitration and condensation with sulfuric acid-formaldehyde mixture have been used for the determination of toluene in biological materials such as tissues, urine and blood (Yant, W. P. *et al.*, 1956).

An ultraviolet spectrophotometric method has recently been described for the analysis of toluene and other alkyl derivatives of benzene in blood (Guertin, D. and Gerarde, H. W., 1960).

Toxicology

Acute toxicity

Liquid toluene is a primary skin irritant. It is poorly absorbed through the intact skin so that systemic intoxication by percutaneous absorption is highly improbable. Contact of liquid toluene with pulmonary tissue (aspiration) will cause chemical pneumonia, pulmonary edema and hemorrhage. Liquid toluene splashed into the eye will burn the cornea if it is not removed promptly by flooding the eye with water. Toluene vapors

ting to the mucous membrane of the respiratory tract. The degree of irritation depends on the concentration and the duration of the exposure.

Acute systemic toluene intoxication is characterized by signs and symptoms of central nervous system depression: headache, dizziness, fainting, weakness, paresthesia, disturbances of coordination and equilibrium, and loss of consciousness. The relationship between toluene vapor concentration in the atmosphere, toluene blood levels and the effects observed in human subjects exposed to toluene for an eight-hour period are summarized in Fig. 54. Fatigue, moderate insomnia and restlessness

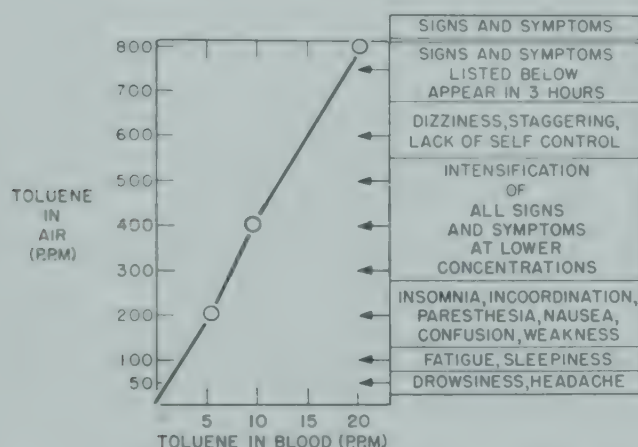


Fig. 54. Correlation of atmospheric toluene concentration with blood toluene and response in man after an 8-hour exposure.

(Gerarde, H. W., 1959; Von Oettingen *et al.*, 1942).

tested for some hours after a continuous exposure of 8 hours to 800 p.p.m. of toluene vapor. Exposure to 800 p.p.m. for 8 hours resulted in severe nervousness, muscular fatigue and insomnia which lasted for several days. Exposures to 100 p.p.m. did not cause the symptoms elicited at the higher concentrations and resulted in any after effects (Von Oettingen, P. A. *et al.*, 1942). Table 35 shows the response of rabbits to high concentrations of toluene vapors.

TABLE 35
RESPONSE OF RABBITS TO 35,000-45,000 P.P.M. TOLUENE VAPOR*

Average time for occurrence (minutes)	Response
2.9	Light anesthesia
9.5	Pupil contracted
11.0	Râles audible
14.8	Loss of blink reflex
16.1	Excitation-running-tremors
40.0	Death

* After Carpenter, C. *et al.*, 1944.

Chronic toxicity

Continued or repeated skin contact with liquid toluene cause dermatitis due to dehydration and removal of the natural fats from the skin. The inhalation of toluene vapors may cause loss of appetite, nausea and vomiting and evidence of central nervous system effects (headache, fatigue, nervousness and somnia). Pain in the chest, nose bleeds, liver enlargement and intolerance to alcohol have also been described in man following repeated exposure to toluene (*API Tox. Rev. Toluene*, 1944).

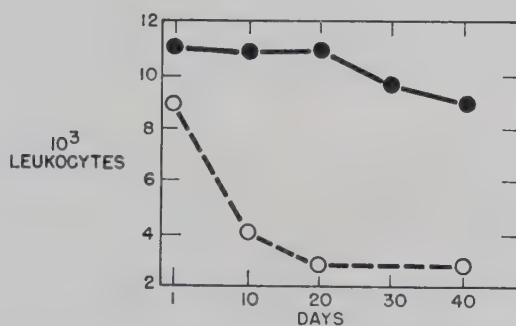
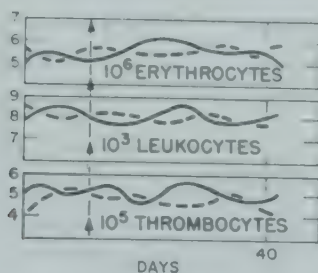


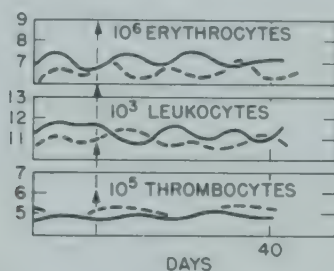
Fig. 55. Comparison of the effect of repeated exposure to toluene and benzene vapor on the leukocyte count of the rabbit. (6.6 and 9.5 mg/l resp., and 6d/wk) — = Toluene; ---- = Benzene.

(Fabre, R. and Truhaut, R., 1944)

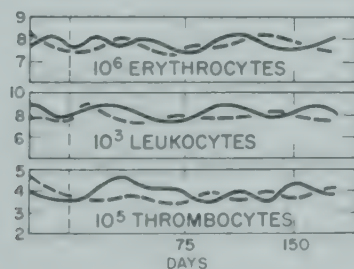
effects produced depend on the vapor concentration and duration of the exposure. Prolonged or repeated exposure to toluene do not cause the severe bone marrow injury and peripheral blood changes that are characteristic of chronic ben-



56. Effect of repeated exposure to toluene vapor on the peripheral blood of the rabbit. (6.6 mg l, 8h d and 6 d wk). — Toluene; - - - Control. (Fabre, R. and Truhaut, R., 1954).



57. Effect of repeated exposure to toluene vapor on the peripheral blood of the rat. (8 mg l, 8h d and 6 d wk). — Toluene; - - - Control. (Fabre, R. and Truhaut, R., 1954).



58. Effect of repeated exposure to toluene vapor on the peripheral blood of the dog. (10 mg l, 4h d and 6 d wk). — Toluene; - - - Control. (Fabre, R. and Truhaut, R., 1954).

zene intoxication (Fig. 55). A temporary, slight lymphocytosis may be observed but there are no significant variations in total leukocyte or differential count. The red blood cells do not appear to be appreciably affected. The extensive animal studies conducted by Fabre and Truhaut clearly indicate that toluene is not a bone-marrow poison (see Figs. 56, 57 and 58). Some commercial toluenes may contain benzene as a contaminant in significant amounts. This is particularly true of toluene derived from coal tar. Because of the insidious effects of low concentrations of benzene on the blood-forming tissues it is important to know if benzene is present in any solvent mixture (Chapter 13, p. 276).

Schmid, E. (1956) has reported on 200 cases of what has been called 'Polishers' keratitis' in workers engaged in spraying furniture with a nitrocellulose lacquer, varnish and thinners containing 20% toluene, 20% butyl acetate, 40% ethyl acetate and butyl alcohol mixture and 20% methyl and ethyl acetate mixture. Under examination by a slit lamp, corneal lesions were found in the area between the eye lids. These lesions are very fine vacuoles, 10 to 40 μ in diameter, round, oval or irregular in shape. The surrounding tissue shows little or no inflammatory reaction and there is a marked disproportion between the actual signs of irritation of the eyes and the symptoms. Pain and photophobia, which are usually most evident in the early morning, tend to subside during working hours. The prognosis is uniformly good, the lesions subsiding after a few days of no exposure without scar formation. The corneal lesion described in 'Polishers' keratitis' has been produced in cats by exposure to vapors of toluene, xylene and methyl, ethyl and butyl acetate. Methyl and butyl alcohol, according to Schmid, did not cause corneal lesions in cats exposed to vapors of these solvents.

n-Butyl alcohol has however been reported to cause corneal lesions in workers exposed to concentrations of 15–200 p.p.m. (Cognan and Grant, 1945).

Chemistry

Liquid toluene is poorly absorbed through the skin but from the gastrointestinal tract the hydrocarbon enters the blood at a much more rapid rate. Toluene vapors are rapidly absorbed by inhalation, so that systemic intoxication can result in a few hours depending on the concentration. Because of the lipid solubility of toluene, the hydrocarbon tends to accumulate in

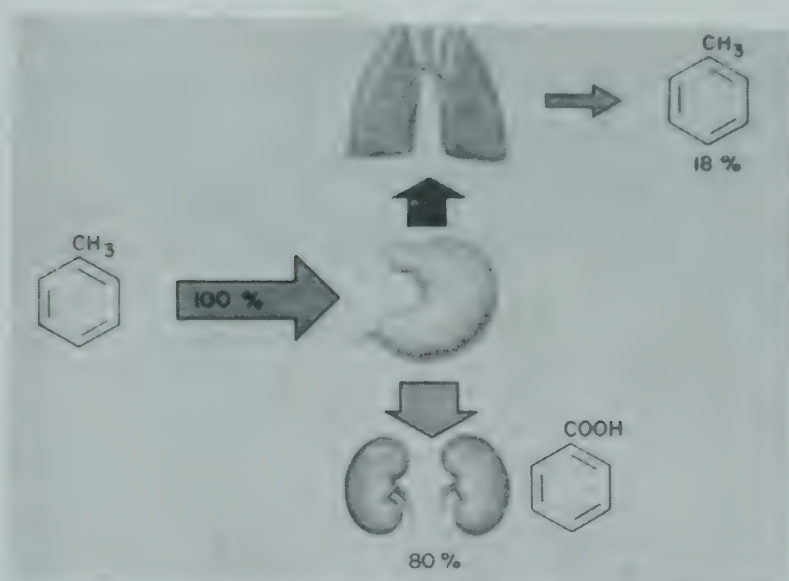


Fig. 59. Elimination and biotransformation of toluene in the rabbit in the 72-hr interval after a single oral dose. The principal urinary metabolite is benzoic acid conjugated with glycine. (Knoop, F. and Gehrke, M. 1925).

fat tissues in proportion to their fat content, as shown in Table 17. Part of the toluene absorbed is exhaled unchanged (see Table 17, p. 59), but most of it is metabolized by oxidation of the side chain to benzoic acid, which is conjugated with glycine in the liver, and excreted as a water-soluble urinary metabolite, hippuric acid. The elimination and biotransformation of toluene in the rabbit is shown in Fig. 59.

Threshold limit

The present threshold limit for toluene in the U.S.A. is 200 p.p.m. This value appears to be excessive, based on the studies with human subjects reported by Von Oettingen *et al.* (1942) which is summarized in Fig. 54. The odor of toluene is readily detected at this concentration but olfactory fatigue quickly follows. No reliance can be placed on the sensory response as a warning of dangerous concentrations, since the limits of sensory acceptability for toluene vapor exceed the toxic limits. The majority of individuals exposed to 300 p.p.m. of toluene complain of eye and throat irritation. Higher concentrations have been tolerated by workmen without complaint. The threshold limit for toluene in the U.S.S.R. is 25 p.p.m.

Prevention, detection and treatment of exposure

(A) Prevention

Exposure to toluene vapors and mists and the liquid hydrocarbon should be minimized by care in handling on the part of the individual worker. In the plant, engineering controls and industrial hygiene practices should be employed to attain this objective.

For the maximum efficiency and comfort of the workers proper ventilation, local exhausts and closed systems for handling and transport of toluene should maintain the atmospheric concentration below the threshold limit of 200 p.p.m. Employees who must be exposed for considerable periods of time to air concentrations in excess of the maximum allowable concentration should be provided with air masks and suitable protective equipment.

(B) Detection

The urinary hippuric acid excretion in a 24-hour urine specimen has been used as a test for exposure to toluene (Teisinger, J. and Srbová, J., 1955). The principal limitation of the test is that hippuric acid is a normal urinary constituent originating

oods containing benzoic acid or precursors of benzoic acid. s high in fruit and vegetables which contain benzoic acid or benzoic acid precursors as quinic acid (especially prunes, berries and plums) increase the hippuric acid output. Quinic is also found in coffee beans. A concentration of 1000 mg hippuric acid per liter of urine has been suggested as a imum allowable concentration for a 24-hour urine sample a value of 3000 mg per liter for an 'end of shift' spot sample ty, F., 1949). According to Teisinger, a 24-hour excretion 1 g of benzoic acid in the urine indicates an exposure to ospheric levels of toluene below 200 p.p.m. for an 8-hour k day. Carpenter *et al.* (1944) reported an increased excre- (7 g above normal) of hippuric acid in the 24-hour urine imen of a human volunteer exposed for 8 hours to 800 p.p.m. oluène vapor.

s an additional precaution and check on working conditions, odic health examinations should be conducted on workers dling toluene. A biennial medical examination should suffice xposure is minimized by the individual worker, if 'good sekeeping" prevails in the plant, and if the vapor concen- on in the working atmosphere is controlled to the safe s described.

he periodic health examination should include an interval ical history, physical examination and complete blood count. he medical history and physical examination particular tion should be focussed on complaints and evidence of eye, ous membrane and skin irritation. Workers exposed to ene who complain of chronic eye irritation should have a lamp examination in order to ascertain if microscopic eal vacuoles are present (Schmid, E., 1956).

Treatment

he treatment of acute vapor exposure to toluene is the same he treatment of acute exposure to any volatile aromatic ocarbon. The victim is removed immediately from the con-

taminated atmosphere. If he has stopped breathing, artificial respiration must be started at once. If the victim is breathing normally and the color of the skin and mucous membranes indicates that oxygenation is satisfactory, no additional treatment is required except to keep the person quiet, warm and rest in a recumbent position. For further details in the medical management of acute intoxication due to aromatic hydrocarbons, see Chapter 6, p. 91.

The signs and symptoms of chronic toluene intoxication consist primarily of irritation of the eye, mucous membranes and skin. In normal individuals removal from further exposure to the hydrocarbon results in complete recovery.

Di-alkyl derivatives of benzene

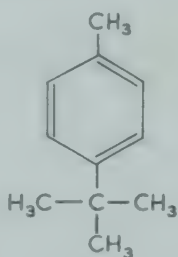
p-*tert*-BUTYLTOLUENE

Synonyms

4-*tert*-butyltoluene, 1-methyl-4-*tert*-butylbenzene, TBT.

Molecular formula: $C_{11}H_{16}$.

Structural formula:



Molecular weight: 148.24.

Physical properties

A clear, colorless liquid with a distinct aromatic odor (see other table on pp. 152 and 153).

Preparation, uses and probable modes of contact

p-*tert*-Butyltoluene (TBT) is made by the alkylation of toluene with isobutylene. The reactants are passed into a stripper which removes excess toluene and after fractionation a TBT heart cut is taken.

This petrochemical has been produced in developmental quantities for use as a stable, high-purity, moderately high-boiling solvent for the preparation of resins. It has also been

suggested as a primary intermediate for synthesis in the chemical and pharmaceutical industry.

Individuals working with *p*-*tert*-butyltoluene may be exposed to low concentrations of hydrocarbon vapor (vapor pressure 0.65 mm of mercury at 25°) aerosols or mists, or in case of accidental spill or leak, have direct skin contact with liquid TBT.

Analytical methods

In general TBT gives the usual chemical reactions of the low alkyl-substituted aromatics such as toluene, ethylbenzene and cumene. Field equipment used for the detection of these aromatic hydrocarbons could be adapted and calibrated for TBT (see Chapter 3). Hine *et al.* (1954) have used an ultraviolet

PHYSICAL PROPERTIES OF THE HYDROCARBON

<i>p</i> -Cymene	
Boiling point	176° C (348.8° F)
Melting point	— 68.2° C (— 90.8° F)
Vapor density (air = 1)	4.62
Vapor pressure	1 mm Hg at 17.3°
Density of saturated vapor-air mixture at 760 mm Hg (air = 1)	1.0048
Per cent in saturated air, 760 mm Hg	0.13 at 17.3° C
Liquid density at 25°/4°	0.86
Index of refraction	1.4904 at 20° C
Solubility	Insol. in water. Miscible with ethanol, etc.
Flash point	117° F (T.C.C.)
Conversion factors (25° and 760 mm Hg)	
1 p.p.m. of vapor	0.00548 mg/l
1 mg/liter of vapor	182 p.p.m.
Flammable limits (Per cent by vol. in air)	0.7 — 5.6

photometric method for the analysis of TBT in air. It is possible to detect concentrations as low as 2 p.p.m. in grab samples of air with this procedure.

There are no published reports on the determination of TBT in biological fluids or tissues. The general methods for the separation of aromatic hydrocarbons from biological samples (extraction, distillation) and subsequent estimation by color reaction or ultraviolet absorption may be used for the analysis of TBT in blood, urine and tissues.

Toxicology

Animal studies

Acute toxicity: Direct contact of the liquid hydrocarbon with pulmonary tissue (aspiration) will cause pulmonary edema and

DISCUSSED IN CHAPTER 9 (FOR XYLENES SEE TABLE 38, PP. 172 AND 173)

<i>p-Tertiary-butyltoluene</i>	<i>m- and p-Vinyltoluene</i>
8° C (379° F)	171° C (340° F) (mixture of isomers)
2.53° F	— 34.5° C (— 30° F) (<i>p</i> -isomer)
	4.08 (mixture)
mm Hg at 25°	1.8112 mm Hg at 25° (<i>p</i> -isomer)
479	1.0079
at 25° C	0.22 at 25° C
75	0.90 at 20° C (mixture)
21 at 20° C	1.5449 at 20° C (<i>p</i> -isomer)
sol. in water (20° C)	Mixture sol. in acetone, carbon tetra-
miscible with ethanol, ether.	chloride, benzene, ether, <i>n</i> -heptane.
	Insol. in water
° F (T.O.C.)	140° F (mixture) (C.C.)
666 mg/l	0.00483 mg/l
0.p.m.	207 p.p.m.
	1.9 — 6.1

hemorrhage. Contact of the liquid hydrocarbon with the skin will remove water and fat from the epidermis which may lead to dermatitis. TBT was found by Hine *et al.* to be a mild rubefacient with a skin irritation score of less than 0.5 according to the method of Draize *et al.* (1946). Systemic intoxication by percutaneous absorption of TBT through the intact skin is highly improbable. Liquid TBT applied to the eyes of rabbits caused heavy discharge and a slight chemosis which disappeared 4 hours after dosing.

The percutaneous LD-50 for rabbits ranged from 13.8 to 27 ml per kilogram of body weight (average = 19.6 ml/kg).

The LC-50 for female rats exposed continuously for 8 hours to TBT vapors is 165 p.p.m. The LC-50 for a one-hour exposure is 934 p.p.m. (female rats), for female rats and mice exposed for 4 hours it is 248 p.p.m. Rabbits exposed to 1000 p.p.m. of *p-tert*-butyltoluene (time not stated) show signs of slight dyspnea but no evidence of central nervous system depression or stimulation. Rats exposed to 1500 p.p.m. showed signs of immediate respiratory distress, which varied from slight nasal discharge to profuse salivation and pulmonary effusion. The majority of animals showed evidence of irritation of the eyes and respiratory tract following exposure to low concentrations of the hydrocarbon vapor (60 p.p.m.). Animals dying from vapor exposure have profuse pulmonary edema and hemorrhage and irritation of the respiratory tract.

The oral LD-50 values for female mice, rats and rabbits are 1.8 ml, 0.9 ml and 2.0 ml respectively per kg of body weight.

In systemic intoxication with TBT, signs of disturbance of the central nervous system predominated in the animal studies reported. These consisted of stimulation and increased motor activity (convulsions) followed by ataxia, confusion, tolerance of side-position and marked depression. Disturbances in muscle tone and flaccid and spastic paralysis of the forelegs and hind legs were also observed. A single oral dose of TBT has produced

permanent paralysis of the forelegs in rats (see Chapter 4, 48).

Chronic toxicity: The mortality in rats receiving 10 one-hour exposures to air saturated with TBT vapor (approximately 10 p.p.m. at 25°) was 80%. There was no evidence of injury or unusual behavior in rats exposed 50 times to 25 p.p.m. or 10 times to 50 p.p.m., other than slightly lowered respiratory rate during the exposure. The duration of the exposure periods ranged from 1 to 7 hours.

Rats exposed daily for 26 weeks to 25 p.p.m. showed no evidence of injury. Three rats out of a group exposed daily for 26 weeks to 50 p.p.m. developed signs of intoxication. After 50 exposures, one rat died, another developed severe flexor contractility of both forelegs after 59 exposures and a third rat showed signs of weakness of the hind legs after 71 exposures to 50 p.p.m. in the air. See p. 51 for further discussion of neurotoxicity due to *p-tert*-butyltoluene.

Pathology: Irritation of the pulmonary tract (pulmonary edema and hemorrhage) was marked in animals exposed to vapors of TBT, but it was also noted after dosing by other routes of administration.

Oral dosing with TBT caused hyperemia of the gastroenteric tract. Liver damage was found in rabbits which received the hydrocarbon percutaneously. This consisted of fatty infiltration which was diffuse or centro-lobular. The following lesions were found in the central nervous system: in the cerebrum, cerebellum and spinal cord there was diffuse edema of the white matter and occasionally acute necrosis, particularly in the corpus callosum and the spinal cord; acute neuronal changes consisting of swelling, vacuolization and chromatolysis in the cortex, hippocampus and cerebellum; in the spinal cord including the medulla oblongata, the nerve cells in the gray columns showed vacuolar changes in the nuclei and also chromatolysis (see Fig. 30, p. 49).

The white and red cell counts in the exposed animals were

lower than normal but are of questionable significance since the values found in control unexposed animals were also abnormally low.

(B) *Human experience*

p-*tert*-Butyltoluene has a distinctive aromatic odor which is readily recognized at an atmospheric concentration of 5 p.p.m. Exposure to a concentration of 80 p.p.m. for 5 minutes will cause eye irritation. Nausea and metallic taste were noted in some human subjects exposed for 5 minutes to concentrations of 20, 60, 80 and 160 p.p.m. One subject complained of giddiness at 160 p.p.m.

Review of the health records of 33 operators assigned to the TBT process over a 5-year period showed that 8 volunteered specific complaints referable to exposure to TBT. The symptoms experienced were nasal irritation, nausea, malaise, headache and weakness. Eight persons presented a cardiovascular syndrome characterized by decreased blood pressure, increased pulse rate and failure to respond to the Master's test in a satisfactory manner. Four individuals showed signs of anxiety and had tremor, and in two operators there was evidence of chemical irritation from contact with TBT. Deviations from normal

TABLE 36

<i>Job classification</i>	<i>No. exposed</i>	<i>Subjective complaints</i>	<i>Altered physiology</i>	
			<i>CV^b</i>	<i>CNS^c</i>
Operators	33	8	10	4
Maintenance men	7	0	0	0
Foremen	4	0	0	0
Professional men	6	2	0	0

^a After Hine, C. H. *et al.* (1954).

^b CV = Cardiovascular.

^c CNS = Central nervous system.

the peripheral blood consisted of decreased hemoglobin and erythrocyte count, leukopenia, eosinophilia, prolonged clotting time and elevated icterus index. A summary of the subjective and objective findings in the group of individuals exposed to TBT is shown in Table 36.

biochemistry

p-tert-Butyltoluene is absorbed into the blood by inhalation of the vapors and after oral administration of the liquid hydrocarbon. There is no information in the literature describing the rates of absorption, elimination and distribution of TBT in tissues. Because of its low vapor pressure it is probable that only a small fraction of the amount absorbed into the blood is exhaled unchanged. The major portion is probably metabolized in the liver and eliminated as water-soluble metabolites in the urine. The urinary sulfate ratio (inorganic/total) is not affected in rats after dosing with TBT (see Table 21, p. 74). This indicates that oxidation of the benzene ring has not occurred. The biotransformations of TBT in the liver probably involve oxidation of the *para*-methyl or one of the methyl groups of the highly branched butyl group. The end products are probably alcohols or carboxylic acids excreted as conjugates with glucuronic acid

PHYSICAL FINDINGS IN WORKERS EXPOSED TO P-TERT-BUTYLTOLUENE^a

<i>Number of individuals having blood abnormality</i>						
<i>Hb</i>	<i>RBC</i>	<i>WBC</i>	<i>Differential</i>	<i>Bleeding time</i>	<i>Clotting time</i>	<i>Icterus index</i>
7	2	6	8	1	5	2
0	0	0	2	0	0	1
1	0	0	2	0	0	0
0	1	1	1	0	0	1

excessive concentrations which are unavoidable because of working conditions or accidents should be provided with suitable respiratory equipment and protective clothing. Skin contact with liquid *p-tert*-butyltoluene should be minimized as much as possible. Impervious gloves should be worn if contact with the hydrocarbon is unavoidable. Clothing that has been wetted with the hydrocarbon should be removed promptly and not re-worn until it has been laundered.

Detection

There is no established test for exposure to *p-tert*-butyltoluene. No biochemical test for detecting latent intoxication due to excessive absorption of the hydrocarbon. It is highly probable that the metabolic transformations of *p-tert*-butyltoluene involve the *para*-methyl group rather than oxidative changes of the *tert*-butyl group. If a sufficiently sensitive method were available for the detection and quantitative analysis of this metabolite, the amount of metabolite in the urine might form the basis for a test of exposure to the hydrocarbon. The validity of the test requires proof that the metabolite is formed in man. In addition, a clinical study must be conducted to determine the relationships between hydrocarbon air concentrations, duration of exposures and the urinary output of the metabolite under normal working conditions.

Periodic health examination should be conducted at regular intervals on workers exposed to *p-tert*-butyltoluene. The medical examination should include brief interval medical history, physical examination and complete blood count.

The physician should direct his attention to signs and symptoms of eye, mucous membrane and skin irritation and to symptomatology referable to central nervous system and cardiovascular involvement (Hine, C. H. *et al.*, 1954). Significant deviations from normal indicating possible effects on the blood forming tissue, central nervous system, or cardiovascular system

is justification for investigation of the working conditions and removing the individuals from possible additional exposure.

(C) Treatment

The first aid treatment and medical management of acute vapor exposure to *p*-*tert*-butyltoluene should be handled as described in Chapter 6, p. 91. Eye, mucous membrane and skin irritation, and systemic intoxication due to chronic exposure to *p*-*tert*-butyltoluene respond favorably to removal of the individuals from further exposure.

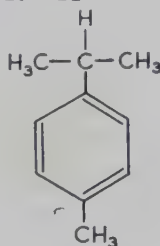
p-CYMENE

Synonyms

p-Isopropyltoluene, paracymol, cymol, *p*-methylisopropylbenzene, 4-isopropyl-1-methylbenzene, cymene.

Molecular formula: $C_{10}H_{14}$.

Structural formula:



Molecular weight: 134.21.

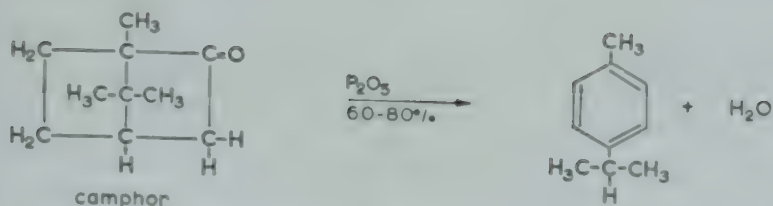
Physical properties

A clear, colorless liquid with an aromatic odor (see further table on pp. 152 and 153).

Sources, uses and probable modes of contact

p-Cymene is a by-product in the manufacture of sulfite paper pulp. It can also be obtained by dehydration and molecular rearrangement of camphor as shown in Fig. 61.

p-Cymene can also be obtained from several other natural isoprenoid substances belonging to the group of terpenes, but the aromatic hydrocarbon itself occurs along with these substances.



51. *Dehydration and molecular rearrangement of camphor to p-cymene.*

ences in many essential oils and in turpentine. This is one of few instances of a natural source of aromatic hydrocarbons other than coal tar and petroleum (See Chapter 2, p. 19).

Cymene is used as a diluent or thinner for lacquers, varnishes and dyes, usually as a constituent of a solvent mixture containing other aromatic hydrocarbons or terpenes.

Contact with *p*-cymene in its present industrial applications may occur by inhalation of vapors and mists and by skin contact with the liquid hydrocarbon.

analytical methods

Cymene undergoes the typical reactions of the alkyl-substituted derivatives of benzene which form the basis for the analysis of the benzenoid hydrocarbons. The concentration of cymene in the atmosphere can be determined with properly calibrated field equipment or by adaptation of the chemical methods described in Chapter 3. The concentration of *p*-cymene in biological fluids and tissues can be determined by adaptation of the chemical or physical methods described for aromatic hydrocarbons after preliminary separation of the hydrocarbon from the sample.

ecology

The toxicological information on *p*-cymene in the published literature is limited to several brief laboratory studies and a clinical report of aplastic anemia of unknown origin in a worker employed in the sulfite paper pulp industry.

Animals are able to tolerate an atmosphere saturated with *p*-

cymene vapors without showing signs of systemic intoxication. The minimal fatal dose for guinea pigs by the intraperitoneal route of administration according to Chassevant and Garreau (1903) is 2.162 g per kg of body weight. Daily doses of 2 g *p*-cymene were administered to dogs with no evidence of adverse effects except diarrhea. Woronow (1929) and Miyamoto (1931) have reported that *p*-cymene does not cause leukopenia or anemia in experimental animals.

p-Cymene is a primary skin irritant which may cause erythema, drying and defatting of the skin; the intensity of these effects depends on the dose and the duration of contact with the hydrocarbon. Liquid *p*-cymene aspirated into the lungs will cause chemical pneumonitis. Since it has a low surface tension and low viscosity, the aspiration of a small volume of liquid *p*-cymene can cause extensive chemical pneumonitis (Gerarde, H. (1959).

Ziegler (1873) found that in man the daily oral administration of 3 to 4 g of *p*-cymene caused nausea, headache and vomiting so that further administration became impossible after 2 or 3 days.

Carlson (1946) reported a case of aplastic anemia in a 56 year old male who was manager of a pulp and paper company for 20 years. Owing to poor ventilation he was exposed almost daily to vapors and was constantly handling and frequently sucking chewing pieces of sulfite pulp. Among the possible toxic materials in a sulfite pulp mill are the relief gases from the digester. The oil-soluble fraction of the relief liquor represents about 4.5 parts in 12,000, of which about 90% is *p*-cymene. Other constituents of relief liquor are: sulfur dioxide, acetaldehyde, acetone, methyl alcohol, acetic acid, formic acid and terpenes.

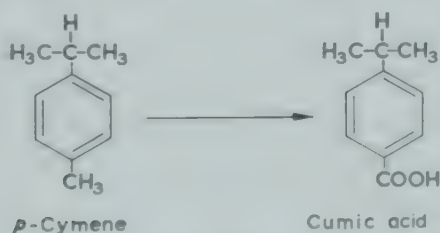
The symptomatology in the case reported by Carlson consisted of progressive weakness, loss of weight, pallor, bleeding from mucous membranes, petechiae, dermatitis and stomatitis. On initial examination the leukocyte count was 1,450, the erythrocyte count 1.6 million and the thrombocytes number

00 per mm³. Histological examination of the sternal bone marrow showed an increased cellularity with many large clusters of immature cells, numerous mitotic figures and moderate numbers of myelocytes and granulocytes. Although Carlson presented this as a case of aplastic anemia, it is not established that the anemia and dyscrasia was of occupational origin. If the aplastic anemia was of occupational origin, the specific etiologic agent remains unknown.

Chemistry

p-Cymene is absorbed into the blood by inhalation of the vapors and mists of the hydrocarbon, and after ingestion and topical application of the liquid to the intact skin. Vallette and others (1954) found that *p*-cymene is absorbed through the intact skin of experimental animals more rapidly than toluene, benzene or ethylbenzene (see Fig. 28, p. 46). Because of its low vapor pressure only a small fraction of the hydrocarbon absorbed into the blood is excreted unchanged. The major part is oxidized in the liver to water-soluble metabolites which are excreted in the urine. *p*-Cymene fed to dogs and sheep is converted to cumic acid. The single methyl group is more readily oxidized than the isopropyl group on the aromatic nucleus. The methyl group on the chain is oxidized to a carboxyl group, as in the case of toluene. The biotransformations of *p*-cymene in the dog and sheep are shown in Fig. 62.

Cumic acid is probably excreted as a conjugate with the amino acid glycine.



2. Biotransformations of *p*-cymene in the dog and sheep.

(Harvey, J. M., 1942).

Threshold limits

The threshold limit for *p*-cymene in the working atmosphere for an 8-hour work day has not been established. Based on analogy with hydrocarbons of similar chemical constitution and the limited toxicological studies reported in animals, 50 p.p.m. appears to be a reasonable level.

Prevention, detection, and treatment of exposure

(A) Prevention

The inhalation of *p*-cymene vapors or aerosols and skin contact with the liquid hydrocarbon should be minimized by careful handling on the part of the individual. In the plant, engineering controls and industrial hygiene practices should be employed to attain the same objective.

The engineering controls, industrial hygiene methods and precautionary procedures for handling volatile aromatic hydrocarbons are discussed in detail in Chapter 8 (Toluene). Although the threshold limit for *p*-cymene has not been established, complaints due to mucous membrane irritation or health hazards are expected if the air concentration is maintained at approximately 50 p.p.m.

(B) Detection

There is no established test which indicates that exposure to *p*-cymene vapor has occurred or that sufficient cymene has been absorbed under actual working conditions to cause sub-clinical intoxication. The detection and quantitative analysis of specific metabolites of *p*-cymene in the urine may serve as the basis for an exposure test. This would be analogous to the use of hippuric acid excretion as a test for exposure to toluene (Chapter 8, Toluene). It is expected that *p*-cymene would be converted *in vivo* to an aromatic carboxylic acid, the transformation probably involving the *para*-methyl rather than the isopropyl group. If the need for an exposure test for *p*-cymene existed, a sensitive method could probably be developed for the quantitation of the metabolite.

analysis of the metabolites of *p*-cymene. To establish the validity of the test, clinical correlation studies would have to be conducted to determine the relationship between the concentrations of hydrocarbon in the air, the duration of the exposure to this atmosphere and the total output of the hydrocarbon metabolites in the urine. The detection of the hydrocarbon itself in the urine would also serve as a test for exposure to *p*-cymene. The sensitivity of the method for the detection of the hydrocarbon would have to be considerably greater than the sensitivity of the method for the analysis of the metabolites because only a small fraction of the hydrocarbon entering the blood is eliminated unchanged in the urine.

Persons exposed to *p*-cymene in their work should have a periodic health examination at regular intervals. This should include interval medical history, physical examination and complete blood count. Complaints of chronic eye, mucous membrane and skin irritation associated with handling of *p*-cymene are sufficient justification for investigating the employees' working conditions. Particular attention should be directed in the physical examination to evidence of local irritation of the mucous membranes and eyes. Although a case of aplastic anemia has been reported in a worker exposed to *p*-cymene vapors (p. 162) there is no evidence that *p*-cymene is a specific bone marrow depressant or myelotoxicant.

Treatment

Acute intoxication due to inhalation of *p*-cymene vapors should be treated in the manner described in Chapter 6, p. 91. Chronic intoxication due to *p*-cymene is expected to present the clinical picture of local irritation of the eyes and mucous membranes and possibly dermatitis. In a normal individual no treatment is necessary other than preventing further exposure to the hydrocarbon. This is done most effectively by removing the worker from the possible source of exposure for a few days and observing the response. If there is no improvement some

other cause should be suspected. In any event the individual should not be permitted to work with *p*-cymene or other chemicals until the diagnosis is made. If the individual appears to be particularly sensitive or susceptible to solvent vapors, he should not be permitted to work in areas where exposure is likely to occur.

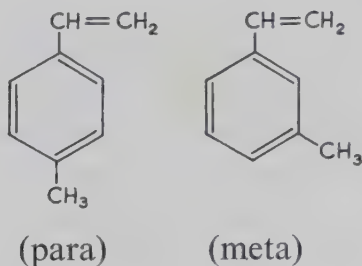
m- AND *p*-VINYLTOLUENE

Synonyms

m- and *p*-Methylstyrenes.

Molecular formula: $\text{CH}_3\cdot\text{C}_6\text{H}_4\cdot\text{CH}:\text{CH}_2$.

Structural formula:



Molecular weight: 118.17.

Physical properties

See table on pp. 152 and 153.

Sources, uses and probable modes of contact

The vinyltoluenes are prepared by the dehydrogenation of *p*-ethyl toluene which is formed by catalytic reforming of virgin naphthas. Toluene can also be ethylated to produce *p*-ethyl toluene which on dehydrogenation gives an isomeric mixture of 65 and 35% of *ortho*- and *para*-vinyltoluene respectively. A *para*-vinyltoluene mixture can also be obtained by condensation of toluene with acetylene to produce ditoluyethane which is then cracked over a kaolin catalyst to the methylstyrene mixture.

p-Vinyltoluene serves as a starting material for synth

ne chemical and drug industry. It may also prove to be the
ce of new plastics and polymers.

he most likely modes of contact with the vinyltoluenes in
r present industrial applications are by inhalation of vapors,
s or aerosols and skin contact with the liquid hydrocarbons.

lytical methods

he vinyltoluenes absorb strongly in the ultraviolet, and
ergo the typical reactions of the mono-cyclic aromatic
rocarbons which form the basis for qualitative and quanti-
ve analytical procedures. These methods can be adapted for
determination of the vinyltoluenes in air and in biological
ls (see Chapter 3).

icology

he most extensive toxicological study on the vinyltoluenes
orted in the published literature is the thorough investigation
ribed by Wolf *et al.* (1956). This study was conducted with
ixture consisting of 55-70% *meta*- and 30-45% *para*-vinyl-
ene.

he results of limited odor and mucous membrane irritation
ies on human subjects are summarized in Table 37. The

TABLE 37
HUMAN RESPONSE TO VINYLTOLUENE VAPOR*

centration (p.p.m.)	Response
400 or more	Very strong odor; strong eye and nasal irritation.
300	Strong objectionable odor.
200	Strong tolerable odor.
50	Odor detectable; no mucous membrane irrita- tion.
10	Odor not detectable.

er Wolf, M. A. *et al.* (1956).

subjects entered a sealed room containing known concentration of the hydrocarbon mixture in the atmosphere and recorded their reactions with respect to odor, eye irritation and nasal irritation.

The direct instillation of the liquid hydrocarbon mixture into the conjunctival sac of the rabbit's eye caused slight irritation of the conjunctival membrane but no corneal injury.

The repeated application of the undiluted hydrocarbon mixture to the ears and shaved abdominal skin of the rabbit caused erythema, blistering and exfoliation of the superficial layer of the skin. Judging by the gross appearance, behavior and body weight of the rabbits during the skin application tests, there was no evidence that the vinyltoluene mixture was absorbed in sufficient quantity to cause acute systemic intoxication.

The approximate oral LD-50 of the hydrocarbon mixture was found to be 4.0 g per kg of body weight for the male albino rat. Post-mortem examination revealed slight hepatic changes and kidney involvement of questionable significance.

Rats, guinea pigs, rabbits and rhesus monkeys of both sexes were exposed repeatedly to vapors of the vinyltoluene mixture for 7-8 hours per day, 5 days a week for as long as 6 months. There were some deaths in the group of rats exposed to 1,130 p.p.m. (6.52 mg/l) of the hydrocarbon vapor mixture after 92-100 exposures each of 7-8 hours duration. There was no mortality in the group of guinea pigs, rabbits or monkeys that received the same number of exposures identical in duration and vapor concentration as described for the rats.

Growth depression and increase in liver and kidney weights were found in the rats and guinea pigs exposed to 1,130 p.p.m. (5.43 mg/l) for 92 to 100 exposures each of 7-8 hours duration. Rabbits treated similarly showed an increase in kidney weight and fatty degeneration in the mid-zonal and central cells of the liver lobule.

There was no evidence of injury to any of the animals used in this study after 92-100 exposures each of 7-8 hours duration.

80 p.p.m. (2.80 mg l) of the hydrocarbon vapor. The mon- appeared to be more resistant than the other species used e no effects were observed at the highest concentration used, 0 p.p.m. (6.52 mg l) for 92-100, 7-8 hour exposures.

most important negative finding in this superb study was absence of any evidence of injury to the blood-forming es. Benzene used as a positive control in these studies caused openia, and splenic and testicular degeneration in animals osed repeatedly to 80-88 p.p.m.

hemistry

here is no information in the literature describing metabolic ies conducted with *m*- and *p*-vinyltoluene. Rats dosed utaneously with a mixture of *m*- and *p*-vinyltoluene (65% a and 35% para) did not show any alteration in the excretion rinary ethereal sulfate (Gerarde, H. W., unpublished data). nalogy with structurally similar alkyl derivatives of benzene etabolic products derived from the biotransformation of inyltoluenes are probably carboxylic acids excreted as con- tes in the urine.

eshold limit

he maximum allowable concentration (MAC) of the vinyl- enes in the atmosphere for an 8-hour workday has been ublished at 100 p.p.m.

ased on the results of toxicological studies on the vinyl- enes with animals, together with the data on experiments human subjects, it is probable that vapor concentrations h will voluntarily be tolerated by most persons will not cause rse systemic effects.

ention, detection and treatment of exposure

Prevention

the atmospheric concentration is maintained at the thresh- old limit and if individual workers are careful to avoid exposure

to the hydrocarbon vapors or liquid, no adverse effects are expected in normal healthy individuals working with vinyltoluene. Additional precautionary measures for handling vinyltoluene are the same as those described in detail for xylene in this chapter.

(B) Detection

There is no established test for exposure to vinyltoluene or a biochemical test for the detection of sub-clinical or latent intoxication due to absorption of the hydrocarbon. Based on metabolic studies conducted with animals with the alkyl derivatives of benzene it is probable that vinyltoluene is converted to carboxylic acids. If the metabolic pathway in man is similar to that found in animals, the urinary excretion of specific carboxylic acids originating from vinyltoluene might be used as a test for exposure to the hydrocarbon. The validity of the test must be established by correlation of vinyltoluene levels in air, the duration of the exposures and the urinary excretion of the metabolites. An exposure test based on the detection of the hydrocarbon in the urine is also theoretically possible. In actual practice it is difficult to measure the microgram quantities of hydrocarbon excreted in the urine.

As a precaution and further check on the efficacy of the preventive methods employed, periodic health examinations should be conducted at regular intervals on workers who may be exposed to vinyltoluene. The medical examination should include a brief interval medical history, physical examination and, if desired, complete blood count. The examination should be focussed on eliciting and detecting symptoms, signs and other evidence of local irritation to the eyes, mucous membranes and skin. Since vinyltoluene is irritating to mucous membranes at concentrations which are believed to be below levels which cause systemic injury, systemic intoxication is highly improbable in the absence of signs or symptoms of mucous membrane irritation.

Treatment

The first aid treatment and medical management of acute intoxication due to inhalation of volatile aromatic hydrocarbons is described in detail in Chapter 6, p. 91.

Mucous membrane, eye and skin irritation which may be associated with chronic vinyltoluene intoxication usually responds favorably to removal of the individual from further exposure.

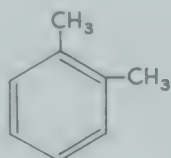
XYLENES

Synonyms

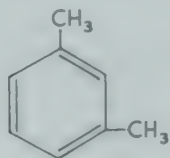
Tolyls, dimethylbenzenes.

Molecular formula: C_8H_{10} .

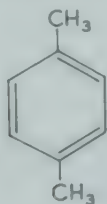
Structural formulae:



o-xylene,
(1,2-dimethylbenzene)



m-xylene,
(1,3-dimethylbenzene)



p-xylene,
(1,4-dimethylbenzene)

Molecular weight: 106.16.

Physical properties

Commercial xylene is a colorless liquid with an aromatic odor. It consists of a mixture of the three isomers of dimethylbenzene boiling in the range of 135-145° (275-295° F). A typical xylene derived from coal tar consists of 15% *ortho*-, 53% *meta*-, 21% *para*-xylene, and 6% ethylbenzene. A typical petrochemical commercial xylene consists of approximately 20% *ortho*-, 44% *meta*-, 20% *para*-xylene, and 15% ethylbenzene. Commercial xylene may contain traces of the following: toluene, phenylthiophene, pyridine and non-aromatic hydrocarbons.

The physical properties of the three isomers of dimethylbenzene are summarized in Table 38.

TABLE 38

	<i>ortho</i> (1,2)
Boiling point	144.414°
Melting point	— 13.3°
Vapor pressure	10 mm Hg at 32°
Vapor density (air = 1)	3.7
Density of saturated vapor at 760 mm Hg (air = 1)	1.03 at 32°
Per cent in saturated air (760 mm Hg)	1.32 at 32°
Liquid density at 25°/4°	0.87583
Index of refraction	1.5058 at 20°
Solubility	Insoluble in water soluble in ethyl alcohol and ether
Flash point	63° F (C.C.)
Conversion factors (25° and 760 mm Hg)	
1 p.p.m. of vapor	0.00434 mg/l
1 mg/l of vapor	230.9 p.p.m.
Flammable limits	
(Per cent by vol. in air)	1.00-6.00

sources, uses and probable modes of contact

Commercial xylene is obtained from the destructive distillation of coal tar and from petroleum. The petrochemical xylenes are produced from catalytically reformed naphthas from which they are removed by solvent extraction. Separation of the xylene mixture into the individual isomers is subsequently accomplished by distillation, fractional crystallization and by other methods.

The xylenes are extensively used as solvents for protective coatings, dyes, inks, and cements; as constituents of aviation gasoline blends, and cleaning fluids; and as starting materials and intermediates for chemical synthesis. Among the most

PHYSICAL PROPERTIES OF THE ISOMERS OF DIMETHYLBENZENE (XYLENES)

<i>meta</i> (1,3)	<i>para</i> (1,4)
102°	138.348°
4.2	55.9
mm Hg at 28.26	10 mm Hg at 27.30
	3.7
at 28°	1.03 at 27.3°
at 28.3°	1.32 at 27.3°
985	0.85666
73 at 20°	1.5004 at 21°
soluble in water, soluble in ethyl alcohol and ether.	Insoluble in water, very soluble in ethyl alcohol and ether.
F (C.C.)	103° F (O.C.)
434 mg/l	0.00434 mg/l
9 p.p.m.	230.9 p.p.m.
7.0	1.1-7.0

important chemicals derived from the xylenes are phthalic acid, isophthalic acid, and terephthalic acid by oxidation of *o*- and *p*-xylene, respectively. These dicarboxylic acids are used in the manufacture of synthetic fibers, plastics and enamels.

The most likely modes of contact with the xylenes in non-commercial use are inhalation of vapor and mists containing the hydrocarbon and skin contact with the liquid. Skin contact may also occur when xylene is used as a solvent, cleaning fluid, and paint-thinner.

Analytical methods

The methods of analysis described in Chapter 3 for benzene and toluene may be used for the determination of xylene in air and in biological fluids.

In the absence of interfering chemicals, field equipment can be calibrated with xylene to measure the concentration of the hydrocarbon in the air directly.

A sensitive laboratory chemical method for xylene consists of collecting the air sample in fuming nitric acid and subsequently extracting the nitrated xylene with butanone. The colored extract is then compared with known nitrated xylene standards (Yant, W. P. *et al.*, 1936).

The analysis of xylene in biological fluids requires a preliminary separation of the hydrocarbon from the sample by distillation or extraction. The determination may then be based on color formation by nitration or treatment of the hydrocarbon with sulfuric acid-formaldehyde mixture.

Toxicology

Acute toxicity

Liquid xylene is a primary skin irritant which causes erythema, dehydration, and defatting of tissue on contact. The type and intensity of the skin reaction depends on the quantity of hydrocarbon and duration of contact. Blistering of the skin may follow prolonged contact with xylene. It is highly improbable

systemic intoxication could result from the percutaneous absorption of xylene through the intact skin.

Liquid xylene is extremely irritating to the eyes and mucous membranes. The aspiration of a few ml of liquid xylene will cause chemical pneumonitis, pulmonary edema and hemorrhage. The ingestion of liquid xylene will cause severe irritation of the gastro-intestinal tract. In animals the intraperitoneal administration of xylene produces a narcosis which is of longer duration than that resulting from benzene or toluene.

The olfactory 'threshold limit' for vapors of *o*-xylene is 7 p.p.m. in air. See p. 40, Table 8. Olfactory fatigue occurs rapidly during exposure so that the odor is no longer detected at this concentration after a few minutes. Concentrated xylene vapors are extremely irritating to the eyes and mucous membranes.

The inhalation of xylene vapors causes a flushing and reddening of the face and a feeling of increased body heat, due to dilatation of the superficial blood vessels. The vapors of xylene are rapidly absorbed into the blood stream and produce signs and symptoms of systemic injury which are primarily referable to the central nervous system, *viz.* fatigue, giddiness, a burning sensation in the head, 'drunkenness' and in severe acute poisoning, loss of consciousness. It appears that the acute toxicity of the xylenes exceeds that of toluene or benzene. The mechanism of action, the effects produced and the pathological changes in acute xylene intoxication are very similar to acute intoxication caused by toluene.

Chronic toxicity

Repeated or prolonged skin contact with liquid xylene will cause drying and defatting of the skin which may lead to dermatitis. Systemic intoxication due to absorption of xylene through the intact skin is highly improbable.

Abre and Truhaut (1954) have conducted the most extensive iterative chronic vapor inhalation study with xylene reported

in the published literature. Rats and rabbits exposed to p.p.m. (3 mg/l) of mixed xylenes 8 hours per day, 6 days week for 130 days had no significant deviations from normal on examination of the peripheral blood. A decrease in

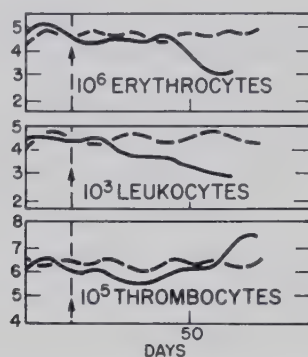


Fig. 63. Effect of repeated exposure to xylene vapors on peripheral blood counts of the rabbit. (5 mg/l, 8h/d and 6d/wk). — = Xylenes; ---- = Control. (Fabre, R. and Truhaut, R., 1955)

number of red and white blood cells and an increase in platelet count was found in rabbits exposed to mixed xylene vapors at a concentration of 1150 p.p.m. (5 mg/l), 8 hours per day, 6 days per week for 55 days (Fig. 63). These changes were much less severe than the hematological effects produced by comparable exposure to benzene.

Cats exposed to the vapors of commercial xylene develop vacuoles in the cornea which resemble the corneal vacuolization ('Polishers' keratitis') found in furniture polishers exposed to solvent vapors. The lesions in the cornea appear under slit lamp examination as very fine oval or irregular vacuoles, 10 to 40 μ in diameter, covering the exposed area between the eye lids. The surrounding tissues show little or no inflammatory reaction. The prognosis is favorable; the lesions tend to subside and recovery is usually complete after a few days free from exposure to xylene.

'Polishers' keratitis' is a non-specific tissue reaction produced

other solvents, such as toluene, and esters of acetic acid, methyl, ethyl and butyl acetate.

In the industrial use of xylene, the most frequent complaints to repeated exposure are headache, fatigue, lassitude, irritability, and digestive disturbances. The latter consist of nausea, anorexia, and flatulence. Examination of a number of printers exposed to xylene vapors suggested that xylene may also affect the heart and vascular system. According to Hirsch (1932) the workers had a low blood pressure, and x-ray of the chest showed dilatation of the aorta and some abnormality in the size and shape of the heart. The hematological examinations of workers exposed to xylene confirm the evidence found in animal experimentation that xylene is not a myelotoxicant. A slight reduction in erythrocyte count and hemoglobin level was found in some individuals, but in general, the hemograms of workers exposed to xylene were within normal limits (Hirsch, S., 1932).

Chemistry

Xylene is rapidly absorbed into the blood by inhalation of vapor or mist containing the hydrocarbon. It is also absorbed in the gastrointestinal tract and to a limited extent after topical application to the intact skin. Because of its fat solubility the hydrocarbon is distributed to the tissues in proportion to their fat content (see Table 19, p. 69).

As with any volatile chemical, part of the xylene absorbed into the blood is exhaled unchanged. Because of its low vapor pressure at body temperature the amount of xylene eliminated through the lung would be small by comparison with the fraction of the dose of toluene or benzene exhaled unchanged (see Table 17, p. 59).

The xylenes are transformed by the liver into water-soluble metabolites which are excreted in the urine as conjugates of glucuronic acid or sulfuric acid.

The biotransformations of the isomers of xylene in experimental animals are shown in Fig. 64.

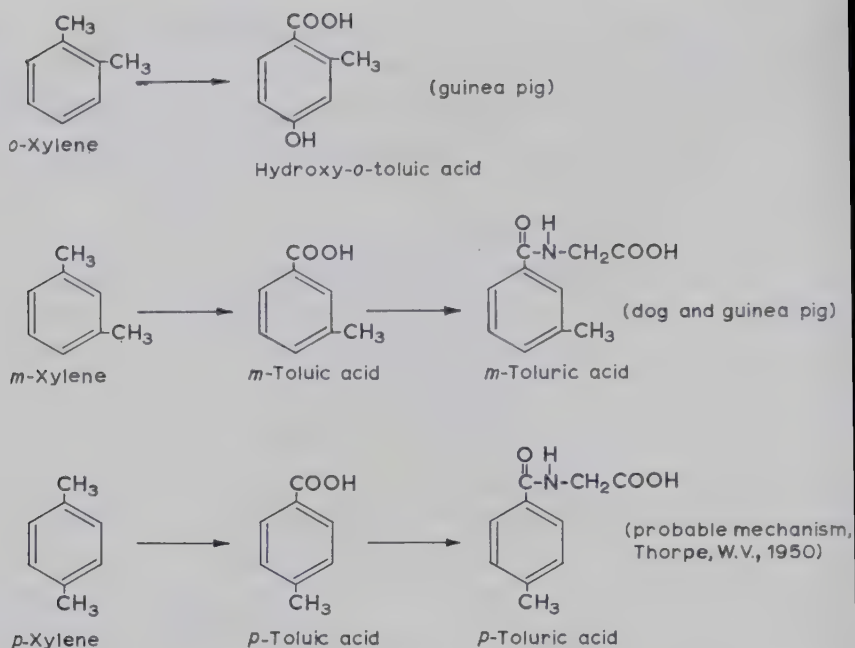


Fig. 64. Urinary metabolites in biotransformation products of xylene isomers in animals. (Williams, R. T., 1950)

Threshold limit

The threshold limit or maximum allowable concentration of xylene for an 8-hour working day has been set at 200 p.p.m. (0.868 mg/l) by the American Conference of Governmental Industrial Hygienists. Some individuals may experience severe eye irritation at this concentration. In addition, there may be some impairment of reaction time in some workers at 200 p.p.m. It appears that 100 p.p.m. is a more acceptable concentration of xylene from the standpoint of comfort and work performance.

Prevention, detection and treatment of exposure

(A) Prevention

The inhalation of xylene vapors and skin contact with liquid hydrocarbon should be minimized by careful handling on the part of the individual worker.

In the plant, good general ventilation, supplemented with

al exhausts in areas where exposure is apt to occur is essential to maintain the air concentration at or below the threshold limit value. Individuals unavoidably exposed to xylene vapor concentrations in excess of the maximum acceptable level should be provided with self-contained oxygen apparatus or with a supplied air type respirator. If skin contact is unavoidable because of the nature of the work, impervious gloves and other protective clothing should be worn by the worker. Adequate washing facilities should also be provided and 'good housekeeping' should prevail throughout the plant.

Detection

There is no established exposure test or biochemical test for detecting latent or incipient toxicity due to absorption of xylene. It is probable that such a test could be developed by application of the newer analytical techniques (chromatography) to detect minute quantities of specific metabolites of xylene. Another possibility is the determination of the hydrocarbon in the urine, which may be present in only μg quantities per liter.

Periodic health examinations should be conducted at regular intervals on workers exposed to xylene. The medical examination should include a brief medical interval history, physical examination, complete blood count, and chest x-ray. In the medical history and physical examination the physician should ask about complaints and evidence referable to irritation of the eyes, mucous membranes and skin, and effects on the cardiovascular system. The latter is based on the report of dilatation of the aorta and abnormality in the size and shape of the heart in workers exposed to xylene (*API Toxicol. Rev., Xylene*, 1948). According to Schmid (1956), persons exposed to xylene who complain of chronic eye irritation should have slit lamp examinations to ascertain if microscopic corneal vacuoles are present.

Treatment

The first-aid treatment and medical management of acute

aromatic hydrocarbon vapor intoxication is described in Chapter 6, p. 91.

Chronic xylene intoxication consists of irritation of the mucous membranes and skin. Radiographic evidence of cardiovascular abnormality may also be present. Normal individuals respond favorably and make a complete recovery if exposure to xylene is discontinued. For relief of symptoms of conjunctivitis due to xylene, astringent lotions containing 0.2% potassium permanganate and cortisone ophthalmic ointment have been found to be effective (Schmid, E., 1956).

Poly-alkyl derivatives of benzene

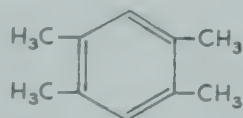
DURENE

Synonyms

2,4,5-Tetramethylbenzene, durol.

Molecular formula: $C_{10}H_{14}$.

Structural formula:



Molecular weight: 134.21.

Physical properties

white odorless solid at room temperature (see further on pp. 182 and 183).

Preparation, uses and probable modes of contact

Durene is one of the three isomers of tetramethylbenzene. The other two isomers are prehnitene 1,2,3,4- and isodurene 1,2,3,5-tetramethylbenzene.

In the past the supply of durene was limited because the aromatic carbon was derived mainly from refinery streams and coke oven distillates, from which it was isolated by distillation and crystallization. Durene, now available commercially, is produced by a synthetic route based on methylation of low boiling aromatics—principally pseudocumene, as shown in Fig. 65.

Durene is a constituent of some aromatic solvents and a minor

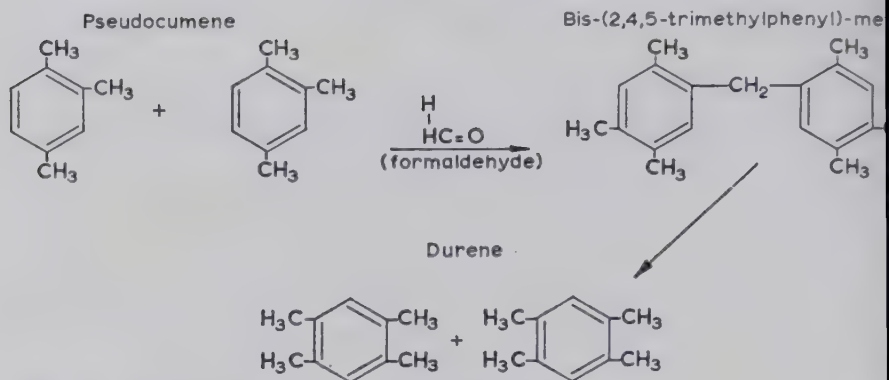


Fig. 65. Synthesis of durene from pseudocumene.

(Hendrickson, J. G. and Wadsworth, F. T., 1954)

PHYSICAL PROPERTIES OF HYDROCARBONS

<i>Durene</i>	
Boiling point	196° C (384.8° F)
Melting point	79.2° C (174.6° F)
Vapor pressure	160 m.m. at 140° C
Density saturated vapor-air mixture at 760 mm Hg (air = 1)	1.78 at 140.1° C
Per cent in saturated air, 760 mm Hg	21 at 140° C
Liquid density	0.838 (81°/4°)
	1.032 (solid)
Index of refraction	1.512
Solubility	Insol. in water. Readily sol. in acetone, ether, benzene. Moderately sol. in alcohols, chlorinated aliph. hydrocarbons, glacial acetic acid
Conversion factors (25° C and 760 mm Hg)	
1 p.p.m. of vapor	0.00548 mg/l
1 mg/liter of vapor	183 p.p.m.
Flash point	130° F (C.C.)
Vapor density (air = 1)	4.6

stituent of motor fuels. It is increasingly used as a starting material for synthesis of polybasic acids for plastics and alkyds and as a source of pyromellitic anhydride for use in cross-linked epoxy resins.

In the present industrial uses, contact with durenene may occur through inhalation of vapors, mists or finely divided dust particles, and by direct skin contact with the solid or liquid durenene as a constituent of solvents.

Physical methods

Durenene undergoes the general chemical reactions typical of

DISCUSSED IN CHAPTER 10

<i>Mesitylene</i>	<i>Pseudocumene</i>
5° C (328.1° F)	169.4° C (337° F)
-2.7° C (— 62.86° F)	— 44° C (— 47° F)
mm Hg at 20° C	341 mm at 140.1° C
5 at 20° C	2.43 at 140.1° C
at 20° C	44 at 140° C
84 (20°/4°)	0.876 (20°/4°)
57 at 20° C	1.50672 at 15.5° C
g/100 ml water.	Insol. in water.
Miscible with alcohol, ether, durenene.	Sol. in alcohol, ether, acetone.
92 mg/l	0.00491 mg/l
p.p.m.	204 p.p.m.
F (C.C.)	112° F (C.C.)
	4.1

the alkyl derivatives of benzene which form the basis for qualitative and quantitative analysis of aromatic hydrocarbons in air, body fluids and tissues. The general physical method for the determination of alkylbenzenes may also be adapted for the analysis of durene (see Chapter 3).

Toxicology

There is very little published information on the mammalian toxicity of durene because until recently the hydrocarbon was available commercially only as one of many constituents of aromatic solvents.

Based on what is known about the physiological effects of hydrocarbons similar in chemical constitution, durene vapor, mist or dust can be expected to irritate the mucous membranes and skin on direct contact. Repeated or prolonged skin contact

TABLE 39

FUNGISTATIC ACTIVITY OF A SATURATED WATER SOLUTION OF DURENE COMPARED WITH OTHER AROMATIC HYDROCARBONS*

<i>Hydrocarbon</i>	<i>Empirical formula</i>	<i>B.p.</i> °C	<i>Radial growth of Fungus</i>
Durene	$C_{10}H_{14}$	190	5%
Diphenyl	$C_{12}H_{10}$	254	16%
Mesitylene	C_9H_{12}	164.5	0
Naphthalene	$C_{10}H_{18}$	218	1%
Acenaphthene	$C_{12}H_{10}$	278	17%
Fluorene	$C_{13}H_{10}$	295	88%
Anthracene	$C_{14}H_{10}$	360	92%
Cymene	$C_{10}H_{14}$	218	2%
Xylene	C_8H_{10}	139	0
Toluene	C_7H_8	110.3	0
Benzene	C_6H_6	80.4	0

* After Bateman, E. and Henningsen (1923).

** *Fomes annosus*.

dehydrate and remove the natural fats of the skin, which result in dermatitis.

The oral toxicity of durene is greater than 5 g per kg of body weight for the rat (Gerarde, H. W., 1959). There were no deaths in 10 animals weighing 200-250 grams dosed with 2.5 ml of a 1% v/v mixture of the hydrocarbon in olive oil. At this dosage there was no evidence of central nervous system involvement or any other indication of systemic intoxication. The animals were normal in behaviour and appearance and gained weight at a normal rate during a 3-week observation period after dosing. Guinea pigs did not develop a sensitivity to durene when injected intradermally according to the procedure described by *et al.* (1951); (Gerarde, H. W., unpublished data).

A saturated solution of durene in water was found to inhibit radial growth of the fungus *Fomes annosus* (Bateman E., Henningsen, C., 1923). The fungistatic activity of durene in comparison with a number of other hydrocarbons is shown in Table 39.

Chemistry

There are no published reports on the absorption, distribution and excretion of durene in experimental animals. There is insufficient information on the polymethyl derivatives of benzene (toluene, mesitylene, pseudocumene) to predict that durene would be absorbed from the gastro-intestinal tract, through the pulmonary alveolar capillaries following vapor or mist inhalation and to a limited extent through the intact skin.

Durene does not alter the quantity of urinary ethereal sulfate excretion after subcutaneous administration of the hydrocarbon (Table 21, p. 75). This indicates that the benzene ring is not hydroxylated by the rat under these conditions. If durene follows the general metabolic pattern of the methyl benzenes it is expected that one of the methyl groups is oxidized to a carboxyl group. The carboxylic acid is subsequently conjugated with the amino acid glycine and excreted in this form in the urine.

Threshold limit

The maximum allowable concentration (MAC) of durene in the working environment for an 8-hour daily exposure has been established.

Based on the extensive toxicological studies and human experience which provided the data for the establishment of threshold limits for other alkyl derivatives of benzene, it is expected that the maximum allowable concentration for durene will be set on vapor levels which cause sensory effects in man rather than the 'no effect' concentrations in animals (W. M. A. *et al.*, 1956). There is no published information describing the relationship between durene vapor concentrations and sensory or mucous membrane effects in man.

Prevention, detection and treatment of exposure

(A) Prevention

Exposure to durene vapors, mists or dusts should be minimized by 'good housekeeping' and careful handling on the part of the individual worker. Engineering controls and industrial hygiene methods should be employed in the plant to attain the same objective.

The limited toxicological information on durene indicates that it has a low order of toxicity, and because it is a solid with a low vapor pressure at room temperature, the hazard associated with its use is also of low order. Engineering controls and industrial hygiene practices should be employed to maintain concentrations of durene below 50 p.p.m. There are no toxicological data or human experience to support the suggestion of 50 p.p.m. as a tentative safe level for repeated exposure to durene. This concentration is suggested on the basis of the chemical constitution of durene and the established threshold limits for other alkyl derivatives of benzene: xylenes, ethylbenzene, styrene, etc. (see Table 23, p. 81). Workers unavoidably exposed to concentrations in excess of this value for prolonged periods should be supplied with suitable respiratory equipment.

protective clothing. Gloves should be worn if the nature of the work makes it impossible to avoid prolonged contact with the hands. Face masks and goggles should be worn to prevent inhalation of durene dust and to prevent eye contact in circumstances where exposure is unavoidable and a dusty atmosphere cannot be prevented.

Detection

There is no established test for exposure to durene or biological test for the detection of incipient toxicity due to extensive absorption of the hydrocarbon.

An exposure test based on the concentration of durene metabolites in the urine is theoretically possible. Sensitive specific analytical methods for detecting the metabolites and correlation with the concentration of hydrocarbon in the air are needed to establish the validity of such a test.

Periodic health examination at regular intervals should be conducted on employees who may be exposed to durene in their work. The physician should keep in mind the possibility of eye, mucous membrane and skin irritation during the course of the interval medical history and the physical examination. The medical examination should include a complete blood count.

Treatment

Acute intoxication by inhalation of durene vapor is highly unlikely except under unusual circumstances, such as accidental release of hydrocarbon at an elevated temperature in poorly ventilated areas or confined spaces. The treatment of acute aromatic hydrocarbon vapor intoxication is described in Chapter 6.

1.

Chronic durene intoxication may present the clinical picture of eye and mucous membrane irritation and dermatitis. This syndrome in a normal individual responds favorably to 'time of time' if the individual is removed from further exposure to the hydrocarbon.

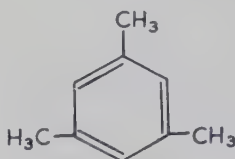
MESITYLENE

Synonyms

sym-Trimethylbenzene, trimethylbenzol, 1,3,5-trimethylbenzene, TMB.

Molecular formula: C_9H_{12} .

Structural formula:



Molecular weight: 120.19.

Physical properties

A colorless, clear liquid with a rather pleasant aromatic odor (see further table on pp. 182 and 183).

Sources, uses and probable modes of contact

Mesitylene is produced commercially by fractionation of coal tar and petroleum distillates. It can also be prepared by dehydrating acetone with sulfuric acid.

Mesitylene is used principally as a major component of certain solvents and paint thinners, which usually contain other isomers of trimethylbenzene, pseudocumene (1,2,4-trimethylbenzene) and hemimellitene (1,2,3-trimethylbenzene). It is also a minor component of other aromatic solvents and motor fuels.

The most probable modes of contact with mesitylene in its present industrial uses are inhalation of vapor and mist, and skin contact with the liquid hydrocarbon.

Analytical methods

The concentration of mesitylene in air can be determined with the direct reading field equipment described in Chapter 3 after calibrating the apparatus for this hydrocarbon. The general chemical methods described for analyzing the alkyl derivatives

benzene may also be adapted for the determination of mesitylene in air.

The concentration of mesitylene in blood, urine and tissues may be determined by application of the general methods of analysis for aromatic hydrocarbons, *viz.* ultraviolet absorption, oxidation, and color formation with sulfuric acid-formaldehyde reagent. The actual analysis is preceded by distillation or extraction to separate the hydrocarbon from the biological sample.

Toxicology

Animal studies

Liquid mesitylene is a primary skin irritant which may cause erythema, drying and defatting of the skin, the intensity of the reaction depending on the quantity of hydrocarbon and the duration of contact with the cutaneous tissue. Systemic intoxication resulting from the percutaneous absorption of mesitylene is highly improbable because, in general, the alkyl derivatives of benzene are poorly absorbed through the skin. The aspiration of liquid mesitylene into the lungs will cause chemical pneumonitis (pulmonary edema and hemorrhage) at the site of contact with pulmonary tissue. Due to its low surface tension a small volume of aspirated hydrocarbon will cover a large area of tissue surface. For this reason, a fraction of a ml of aspirated mesitylene can cause extensive pulmonary injury (see Chapter 4, Section 13).

The mortality in rats dosed orally with 5 ml of mesitylene per kg of body weight was 1/10. For purpose of comparison, the mortality in rats receiving 5 ml of benzene and 5 ml toluene per kilogram of body weight was 0/10 and 3/10 respectively. See Table 14, p. 56 and Table 16, p. 58. An intraperitoneal dose of 3 ml of mesitylene was found to be lethal for guinea pigs. Single intra-peritoneal doses of 9 to 12 ml of mesitylene per kg of body weight invariably resulted in death within 24 hours in guinea pigs. The approximate lethal intraperitoneal dose for a rat is 1.5-2 ml (Spector, W. S., 1956). Cameron *et al.* (1938)

reported that rats survived single subcutaneous doses of 12 ml of mesitylene per kilogram of body weight. Hultgren (19) found that daily subcutaneous injections of 0.12 ml of mesitylene in rabbits for 3 to 5 days caused no change in the peripheral blood leukocyte count. Doses of 0.2 ml caused a transient leukopenia, and 2.5 ml per kg of body weight caused a temporary leukopenia and thrombocytopenia. A single subcutaneous dose of 8-10 ml of mesitylene per kilogram of body weight produced leukocytosis in rats, whereas a comparable dose of benzene caused a profound leukopenia 96 hours after dosing (Gerat H. W., unpublished data).

Mice exposed to mesitylene vapors at concentrations ranging from 25 to 35 mg/l (5000-7000 p.p.m.) are sedated and tolerate the side position. At higher concentrations, 35 to 45 mg/l (7000-9000 p.p.m.), there is a loss of reflexes in addition to central nervous system depression. The duration of the exposures in these atmospheres is not stated (Lazarew, N. W., 1929).

Cameron *et al.* (1938) observed that rats receiving a single continuous 24-hour exposure to 3 mg of mesitylene per liter (611 p.p.m.) showed no evidence of adverse effects. Rats also tolerated the same air concentrations of mesitylene for 14 days of exposures of 8-hours duration with no apparent signs of injury. When the concentration of mesitylene was increased to 12 mg/l (2400 p.p.m.), 4 out of 16 rats died from a single continuous 24-hour exposure. During the exposure the animals showed signs of central nervous system depression and died of respiratory failure. Post-mortem examination revealed congestion in the lungs but no other evidence of tissue pathology.

Rossi and Grandjean (1957) exposed rats to 1700 p.p.m. vapors derived from a solvent mixture of 30% mesitylene and 50% pseudocumene (1,2,4-trimethylbenzene) for 10 to 21 days. Although these investigators were primarily interested in the excretion of phenols in the urine of these rats, they reported no fatalities or other adverse toxicological effects in the animals. The biochemical findings in the urine of these animals

discussed in the section on biochemistry, p. 193. Bättig *et al.* (1958) exposed rats to 1700 p.p.m. of vapors of the mixture of mesitylene and pseudocumene for 4 months. This study is described in detail in the section on pseudocumene in this chapter.

Human experience

Bättig, Grandjean and Turrian (1956) reported the results of their investigations on 27 persons who had worked for a number of years with a solvent called 'Fleet-X-DV-99' which consisted of 30% mesitylene and 50% pseudocumene (1,2,4-trimethylbenzene). Other hydrocarbons reported in this solvent were: traces of hemi-mellitene (1,2,3-trimethylbenzene), 1-methyl-2-methylbenzene and 1-methyl 4-ethylbenzene. The concentration of benzene in 'Fleet-X-DV-99' is not stated, although 95-98% of the hydrocarbons in the solvent had a boiling range of 160-165°.

Clinical examination revealed that a significant number of individuals exposed to 'Fleet-X-DV-99' had symptoms and signs of nervousness, tension and anxiety and 'asthmatic-bronchitis'. Examination of the peripheral blood showed a tendency to hypochromic anemia and a deviation from normal of the coagulability of the blood. These authors attribute the clinical and laboratory findings in these workers to exposure to 1,2,3-trimethylbenzene isomers, mesitylene and pseudocumene. The concentration of hydrocarbon vapors found in the atmosphere in this study ranged from 10-60 p.p.m.

This is the only published report of human exposure to mesitylene in combination with other hydrocarbons and possibly unidentified chemicals. In naming the etiologic agent in suspected occupational disease one must be aware of the 'post-hoc' fallacy in any clinical study of this type. The earlier clinical studies on toluene and the xylenes suggested that these hydrocarbons are myelotoxicants which affected the blood-forming tissue. It appears in retrospect that the small proportion of benzene

present as a contaminant in these solvents was probably responsible for the abnormalities reported in the peripheral blood of the individuals exposed.

Biochemistry

Mesitylene vapors and mists of the hydrocarbon are readily absorbed into the blood by inhalation. Liquid mesitylene is absorbed into the blood from the gastrointestinal tract and subcutaneous and intraperitoneal dosing. There are no studies in the published literature describing the rate of percutaneous absorption of mesitylene. By comparison with other routes of administration, the rate of absorption through the intact skin is probably considerably slower.

The major portion of mesitylene in the blood is excreted in the urine as water-soluble metabolites. A small fraction of absorbed hydrocarbon is probably exhaled unchanged. Mesitylene is oxidized in the dog and guinea pig to mesitylenic

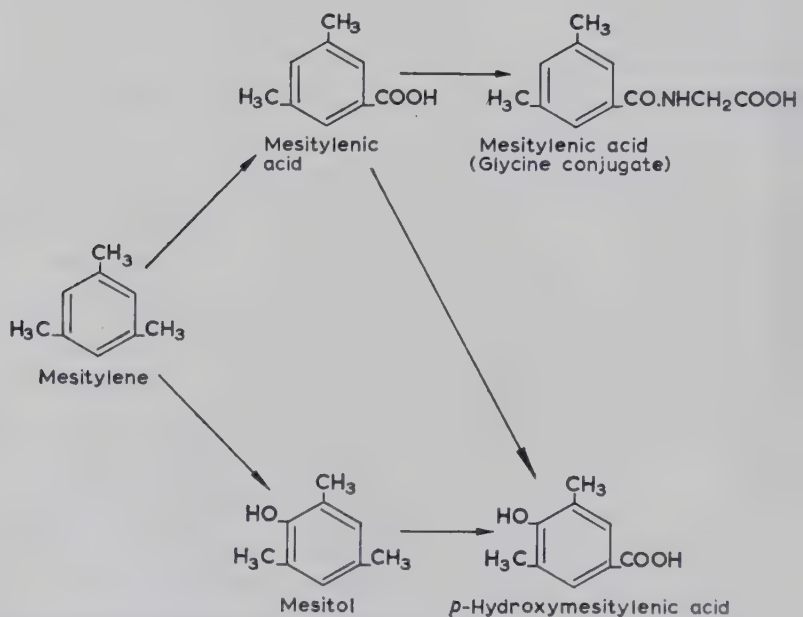


Fig. 66. Biotransformations of mesitylene in the dog and guinea pig.
(Williams, R. T., 1971)

h is excreted partly free and partly combined with the amino glycine. Mesityl and *p*-hydroxymesitylenic acid have also been identified in the urine of animals dosed with mesitylene. Subcutaneous administration of mesitylene to rats increased urinary excretion of ethereal sulfate indicating that hydroxylation of the hydrocarbon had taken place (Table 21, p. 74). This is in agreement with the observation that exposure to vapors of mesitylene increased the urinary output of phenols (Sato, L. and Grandjean, E. 1957). The biotransformations of mesitylene in animals are shown in Fig. 66.

Threshold limit

The threshold limit for mesitylene in the working atmosphere has not been established. On the basis of the toxicological studies reported in the literature, and the threshold limits already established for alkyl derivatives of benzene, 50 p.p.m. appears to be a reasonable figure. Bättig *et al.* (1958) have suggested a threshold limit of 35 p.p.m. for mesitylene for an 8-hour work

Prevention, detection and treatment

Prevention

The general precautionary measures described in Chapters 7 and 8 for controlling and limiting exposure to the volatile aromatic hydrocarbons should be employed in any industrial process involving large quantities of mesitylene. If the concentration of mesitylene in the plant atmosphere is maintained below the suggested threshold limit of 35-50 p.p.m., no complaints of mucous membrane irritation or health hazard due to absorption of the hydrocarbon are anticipated. The individual worker, foreman or technician should also be careful in handling mesitylene to avoid unnecessary inhalation of the vapors or skin contact with the liquid hydrocarbon.

(B) Detection

There is no established test which indicates that exposure to mesitylene vapor has occurred or that sufficient mesitylene has been absorbed under actual working conditions to cause sub-clinical or incipient toxicity. Since the urinary output of phenols is increased in animals exposed to mesitylene vapor and the urinary sulfate ratio is decreased after subcutaneous injection in animals, these biochemical alterations may provide the basis for a useful test for exposure to the hydrocarbon vapor. The validity of the test must be established by clinical studies which show correlations between hydrocarbon vapor concentration, exposure times and urinary excretion of phenols or alterations in the urinary sulfate ratio. More difficult, but theoretically possible, is a test based on the quantity of mesitylene present in the urine of exposed individuals. The difficulty in this case is the great sensitivity required to detect microgram quantities of hydrocarbons in urine.

A health examination should be conducted at periodic intervals on individuals who might be exposed to mesitylene in the work environment. The medical examination should include a brief history, medical history, physical examination and a complete blood count. Complaints or evidence of local irritation of the mucous membranes or eyes, is justification for investigation of the work environment. The report of blood abnormalities in workers exposed to a solvent mixture containing mesitylene emphasizes the importance of the complete blood count. Individuals showing significant deviations from normal in the peripheral blood should be removed from further exposure to mesitylene. The hematological values given in Chapter 7, p. 194, suggest what is meant by a significant deviation from normal. Individuals exposed to mesitylene presenting symptoms or signs of respiratory difficulty should have chest X-rays.

Treatment

ate intoxication due to inhalation of mesitylene should be treated as an emergency as described in Chapter 6.

Acute mesitylene intoxication manifested in the form of irritation of the eyes, nose and mucous membranes or symptoms of pulmonary irritation responds favorably after the individual is removed from further exposure. The abnormalities described in the peripheral blood in individuals exposed to excessive atmospheric concentrations of mesitylene for long periods of time are also reversible simply by removing the individual from further exposure to the hydrocarbon.

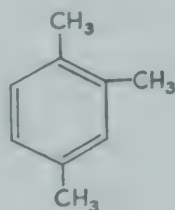
PSEUDOCUMENE

Synonyms

pseudocumol, 1,2,4-trimethylbenzene, *as*-trimethylbenzene.

Molecular formula: C_9H_{12} .

Structural formula:



Molecular weight: 120.19.

Physical properties

Colorless liquid having an aromatic odor (see further table 6, 182 and 183).

Preparation, uses and probable modes of contact

Pseudocumene is produced by catalytic cracking of heavy oil and catalytic reforming of virgin naphtha. It can be obtained in high purity by conventional distillation of a C_9 aromatic hydrocarbon reformat fraction. See Table 4, p. 16.

Pseudocumene is also produced by distillation of heavy tar naphtha fractions.

Pseudocumene is encountered commercially as a constituent of aromatic solvents (*e.g.* Solvesso 100, see p. 277) and fuels. Technical pseudocumene and heavy coal tar naphtha containing 30% pseudocumene have found limited use as vermifuge. It may attain commercial importance in the future as a starting material for the synthesis of durene (1,2,4,5-tetramethylbenzene) and other chemicals.

The probable modes of contact with pseudocumene in present industrial applications are by inhalation of vapors and skin contact with the liquid hydrocarbon itself as a constituent of aromatic solvents.

Analytical methods

The concentration of pseudocumene in the atmosphere can be determined with the direct-reading field equipment described in Chapter 3. The general physical and chemical laboratory methods of analysis described for the alkyl derivatives of benzene may be adapted for the analysis of pseudocumene in air and biological samples (tissues, blood, urine).

Toxicology

(A) Animal studies

The toxicological studies reported in the literature on pseudocumene are limited because the hydrocarbon has not attained commercial importance except as a constituent of aromatic solvents.

The aspiration of liquid pseudocumene will cause chemical pneumonitis, pulmonary edema and hemorrhage (Gerard W., unpublished observations).

Cameron *et al.* (1938) found that the minimal fatal dose of pseudocumene for guinea pigs by the intra-peritoneal route of administration was 1.5-2 ml per kg of body weight.

The mortality in male rats dosed orally with 5 ml per

body weight was 3-10. See Table 16, p. 58. Post-mortem examination showed generalized vaso-dilatation, hyperemia of gastrointestinal tract and pulmonary hemorrhage. Animals receiving this dose made a complete recovery without sequelae 2 weeks after administration of the hydrocarbon (Gerarde, V., 1959).

Mice exposed to pseudocumene vapors at a concentration of 100 mg per liter (approximately 8100 p.p.m.) for an undisclosed period of time developed loss of reflexes, narcosis, and tolerated inversion position (Lazarew, N. W., 1929).

Repeated or prolonged skin contact with liquid pseudocumene caused drying, scaling and fissuring of the skin, although it is highly improbable that systemic intoxication could result from the percutaneous absorption of the hydrocarbon.

Cameron *et al.* (1938) found no evidence of injury in rats exposed to vapors of pseudocumene at a concentration of 10.8 mg per liter (approximately 2000 p.p.m.) for fourteen 8-hour periods.

Horowitz (1929) injected rabbits subcutaneously each day for three weeks with 2 to 3 g of pseudocumene dissolved in olive oil. Examination of the sites of injection revealed local irritation, inflammation, and necrosis of subcutaneous tissue. Histological examination showed moderate reduction in erythrocyte count, similar to that seen in animals dosed with toluene, xylene, and a slight leucocytosis.

Hittig *et al.* (1956) studied the toxicity of a commercial solvent mixture (Fleet-X-DV-99) consisting of 50+ % pseudocumene, 40 % mesitylene (1,3,5-trimethylbenzene) and small amounts of the three isomers of methyl-ethylbenzene. The intraperitoneal LD₅₀ of the solvent mixture for the rat was found to be 2.6 g of body weight. Rats exposed to 1700 p.p.m. of solvent mixture for approximately 4 months did not increase in body weight as rapidly as the controls during the experimental period. The greatest difference in body weight between the control and experimental animals was found about 3 weeks after the start

of the experiment. During this interval there was a marked difference in the daily food consumption in the two groups of animals. This difference in food consumption diminished at the 3rd week of the experiment and the growth curves of the two groups of animals were essentially parallel.

No hematological abnormalities were found in the animals during the first 3 weeks of exposure to 1700 p.p.m. of hydrocarbon solvent vapor. Thereafter, the experimental animals showed a progressively increasing relative lymphopenia and neutrophilia as compared with the control animals. No evidence of injury to blood forming tissues was found in the animals.

The hydrocarbon vapors caused a marked depression of the central nervous system but no deaths were reported in any group of exposed animals. The water consumption and urine output of the experimental animals was significantly greater than normal. Post-mortem examination of animals sacrificed at the end of 4 months of exposure revealed fatty changes in the liver, hyperemia of the lungs and thickening of the alveolar walls.

B. Human experience

Battig *et al.* (1958) have reported the results of a clinical investigation of 27 men exposed to 10-60 p.p.m. of Fleet-X-DV. A considerable number were found to have a hyperchromic anemia, chronic bronchitis, abnormal blood coagulation, and evidence of central nervous system depression. Details of the study are given in Chapter 10 (Mesitylene, p. 191).

Biochemistry

Pseudocumene is absorbed into the blood from the gastrointestinal tract, after inhalation of vapors and mists and at a much slower rate after topical application of the liquid hydrocarbon to the intact skin. As with the other alkyl derivatives of benzene, it is distributed by the blood to the tissues in proportion to their fat content.

According to Jacobsen the *p*-methyl side chain of pseudocumene is oxidized to carboxyl to form *p*-xylic acid which is excreted in the urine (Williams, R. T., 1947). This conversion, shown in Fig. 67, probably takes place in the liver.

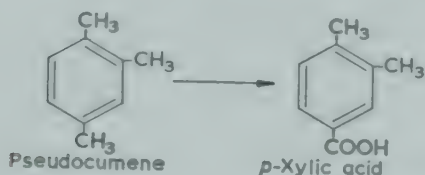


Fig. 67. Biotransformation of pseudocumene (1,2,4-trimethylbenzene).
 (After Jacobsen cited in Williams, R. T., 1947).

After the subcutaneous administration of pseudocumene in rats increased slightly the urinary excretion of ethereal sulfate (see page 21, p. 74). This indicates that hydroxylation of the benzene ring has occurred. The phenolic compound is conjugated with glucuronic acid and is excreted in this form in the urine.

Threshold limit

The maximum allowable concentration (MAC) for pseudocumene in the working atmosphere for an 8-hour work day has not been established.

Prevention, detection and treatment of exposure

The discussion presented in the section on *Prevention, detection and treatment of exposure* to mesitylene is directly applicable to pseudocumene. It appears that pharmacologically and toxicologically these two isomers of trimethylbenzene are very similar. Specific metabolites formed from pseudocumene would not be the same as the metabolites of mesitylene. The general discussion relating to the possibility of using the urinary excretion of metabolites or of the hydrocarbon itself to detect exposure is also applicable to pseudocumene.

Dicyclic and tricyclic aromatic hydrocarbons

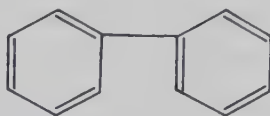
DIPHENYL

Synonyms

Biphenyl, phenylbenzene, xenene.

Molecular formula: $C_{12}H_{10}$.

Structural formula:



Molecular weight: 154.20.

Physical properties

A white solid having a flake-like appearance and a strong odor at room temperature (see further table on pp. 202 and 203).

Sources, uses and probable modes of contact

Diphenyl is produced by the thermal dehydrogenation of benzene: $2 C_6H_6 \rightarrow C_6H_5 \cdot C_6H_5 + H_2$. In one process it is manufactured by passing benzene vapor through an iron tube packed with pumice or other contact substance, at temperatures in the range of 650-800°. In another process benzene vapors are passed through molten lead.

Diphenyl is one of the most thermally stable of known organic compounds. This forms the basis of its use either alone or mixed with diphenyl oxide as a low pressure, high temperature heat transfer medium. Diphenyl is used as a heat transfer fluid

icularly as a component of Dowtherm A, a eutectic mixture containing 26.5% diphenyl and 73.5% diphenyl oxide. The mixture is fluid above 12° and can be used without deterioration at operating temperatures up to 400°. Diphenyl is also used as a fungicidal agent particularly for citrus fruits, lemons, grapefruit and oranges. A tolerance of 110 p.p.m. has been established in the United States for diphenyl on citrus fruit skin.

The most probable mode of contact with diphenyl in industry is the exposure of personnel to vapors or fumes in case of a leak in the heat-transfer system containing the hydrocarbon. Skin contact with diphenyl may also occur in the use of the hydrocarbon as a fungicidal agent.

Physical methods

Diphenyl undergoes the general chemical reactions characteristic of aromatic hydrocarbons. It absorbs strongly in the violet which has formed the basis for the analysis of diphenyl in water. Diphenyl in hexane absorbs maximally at 28.5 μ giving a strong deflection with a 0.001% solution in a 1-cm quartz cell. In the absence of interfering aromatic hydrocarbons, the general methods of analysis described for naphthalene and benzene in air and biological fluids may be adapted for the quantitative analysis of diphenyl.

Toxicology

Acute toxicity

The most extensive toxicological study on diphenyl in the published literature is the work reported by Deichmann *et al.* (1970).

Diphenyl applied directly to the intact skin of rabbits caused minimal local tissue reaction at the site of contact. A single dose of diphenyl in olive oil administered orally to rabbits caused an increase in respiratory rate, lachrymation, loss of appetite and body weight, muscular weakness, unsteadiness, respiratory difficulty, coma and death 2 hours to 18 days after

PHYSICAL PROPERTIES OF HYDROCARBONS

	<i>Diphenyl</i>	<i>Indene</i>
Boiling point	255° C (491° F)	182.57° C (360° F)
Melting point	70° C (158° F)	—1.64° C (29.1° F)
Vapor pressure	9.46 mm Hg at 115° C (239° F) 71.85 mm Hg at 166° C (330.8° F) 284.0 mm Hg at 210° C (410° F)	1.7 mm Hg at 25° C (77° F) 6.7 mm Hg at 50° C (122° F)
Vapor density	5.31	4.01
Density of saturated vapor-air mixture at 760 mm Hg (air = 1)	1.02 at 115° C	1.0066
Per cent in saturated air, 760 mm Hg	1.24 at 115° C	0.22
Liquid density	0.991 (750°/4°)	0.9924 (25°/4°)
Index of refraction	1.588	1.5740
Solubility	0.8 mg/100 ml water at room temp.	Miscible with alcohols, ethers, arom. hydrocarbons.
Flash point	235° F (C.C.)	173° F (ASTM)
Flammable limits		0.9 (lower limit)
Autoignition temp.	498° C	
Conversion factors (25° C, 760 mm Hg)		
1 p.p.m. of vapor	0.00524 mg/l	0.00474 mg/l
1 mg/liter of vapor	191 p.p.m.	210 p.p.m.

D IN CHAPTER 11

<i>β-Methyl-naphthalene</i>	<i>Naphthalene</i>	<i>Tetralin</i>	<i>Anthracene</i>
<i>C</i> (<i>α</i>)	217.9° C (424.2° F)	207.2° C (405° F)	342° C (648° F)
<i>C</i> (<i>β</i>)			
<i>C</i> (<i>α</i>)	80.22° C (176.4° F)	—30° C (—22° F)	217° C (422.6° F)
<i>C</i> (<i>β</i>)			
<i>nethyl</i>			
7	approx. 0.082 mm Hg at 25° C (77° F)	1 mm Hg at 38° C (100.4° F)	1 mm Hg at 145° C (293° F) 100 mm Hg at 250° C (482° F) 760 mm Hg at 342° C (648° F)
	4.4	4.6	6.15
64° C (<i>α</i>)	1.00 at 25° C	1.036 at 38° C	1.076 at 145° C
61° C (<i>β</i>)			
7° C (<i>α</i>)	0.01 at 25° C	0.13 at 38° C	0.13 at 145° C
5° C (<i>β</i>)			
(20°/4°) (<i>α</i>)	1.145 (20°/4°)	0.971 (20°/4°)	1.25 (27°/4°)
(20°/4°) (<i>β</i>)			
(20° C) (<i>α</i>)		1.54614 (20.2° C	
(40° C) (<i>β</i>)			
in water.	3 mg/100 ml water at 20° C. 4.29 g/100 ml ethanol at 20° C.	Insol. in water. Very sol. in ethanol, ether.	Insol. in water. 1 g dissolves in 67 ml abs. ethanol, 70 ml CH ₃ OH, 62 ml benzene, 85 ml CHCl ₃ , 200 ml ether, 31 ml CS ₂ , 86 ml CCl ₄ , 125 ml toluene.
in alcohol,			
ndronaphtha-	Very sol. in ether.		
d fised and			
oils.			
(C.C.) (<i>α</i>)	176° F (C.C.)	171° F (O.C.)	250° F (C.C.)
(C.C.) (<i>β</i>)		180° F (C.C.)	
	0.88-5.9		881° F
mg/l	0.00541 mg/l	0.00541 mg/l	0.00728 mg/l
n.	183 p.p.m.	183 p.p.m.	137 p.p.m.

dosing. The single lethal oral dose administered as a 25% preparation in olive oil was 2.41 g per kg for the rabbit and 3.2 per kg for the rat. The oral administration of diphenyl caused little or no local tissue injury except for some slight irritation of the stomach, duodenum, and upper jejunum of animals which succumbed a few hours after ingestion of the hydrocarbon. The principal toxic effects were found in the liver and kidneys. These consisted of moderately severe albuminous and fatty hepato-cellular degeneration and severe renal changes characteristic of glomerular tubular nephritis. Slight to severe toxic degenerative changes were also found in the myocardium. Animals surviving a single oral dose of diphenyl were found to have pulmonary congestion, pulmonary edema, lobular and interstitial pneumonitis. A mild paralysis of the hind legs and asphyxial convulsions were observed in some animals.

There are no published reports describing the relationships between the concentration of diphenyl in air and sensory or mucous membrane effects in human subjects. Concentrations of 3 or 4 p.p.m. of Dowtherm A are irritating to the eyes and mucous membranes of the nose and throat, and produce a burning and smarting sensation which disappears rapidly when exposure is terminated (Dow Chemical Co., 1950).

The acute toxic concentration of Dowtherm A vapor to animals could not be established due to the low vapor pressure of the chemical mixture.

Liquid Dowtherm A may be somewhat irritating and painful to the eye, but according to available evidence, it does not cause serious injury.

No acute intoxications in man due to diphenyl or Dowtherm A have been reported in the literature.

Chronic toxicity

The repeated application of purified or technical diphenyl to the abdominal skin of rabbits did not induce evidence of local irritation (Deichmann, W. B. *et al.*, 1947). The diphenyl

is applied as a 25% preparation in olive oil 5 consecutive days 2 hours each day and washed off with soap and water at end of the exposure period. The daily dose of hydrocarbon applied to the intact skin was 0.5 g per kg of body weight. Some fatalities occurred and all the rabbits showed a subnormal gain in body weight, due to percutaneous absorption of the hydrocarbon. Minimal changes in the heart, liver and kidneys were found on post-mortem examination. Histological examination of the spleen revealed some follicular atrophy, necrosis, and leukocytic infiltration.

Rabbits were dosed by stomach tube two or three times each week with 1 g of diphenyl dissolved in olive oil. The total oral dose in these animals ranged from 4 to 21 times the single oral dose ($LD_{50} = 2.41 \text{ g/kg}$). The repeated oral administration of sublethal doses of diphenyl did not induce significant changes in the number of erythrocytes, the number or types of leukocytes or the hemoglobin content of the blood. Retention of urea nitrogen in the blood occurred near the terminal stage of the intoxication in most of the rabbits dosed with diphenyl. Weanling rats fed 1% diphenyl in a diet containing 6% casein for approximately 30 days showed an inhibition of growth rate as compared with the control animals (West, H. D. and Jefferson, G. C., 1942).

The repeated feeding of daily doses of 50 and 100 mg of diphenyl for 2 months induced moderate degenerative changes in the liver and kidneys in rats. These changes were not increased in severity in rats fed for periods up to 13 months. Thyroid and parathyroid functions appeared enhanced. Two out of 13 rats repeatedly dosed with diphenyl developed papillomata of the forestomach. An additional rat was found to have a squamous carcinoma of the forestomach (Pecchiai, L. and Saffiotti, U., 1967).

Rabbits, rats and mice were used by Deichmann *et al.* to investigate the toxicity of diphenyl dust by inhalation. Rats were dosed for 7 hours per day, 5 days a week for a maximum of

64 days. The inhalation of dust composed of 50% diphenyl on Celite (diatomaceous earth) in a concentration of 0.30-0.04 mg of diphenyl per liter of air caused irritation of the nasal mucosa, respiratory difficulty and death in some of the rats exposed. Post-mortem examination revealed severe bronchopulmonary lesions and minimal toxic effects in the kidneys and liver. Rabbits were apparently more resistant to diphenyl dust since they showed no evidence of local or systemic injury following repeated exposures to the same quantities to which rats were exposed.

Mice receiving 62 seven-hour exposures to 0.005 mg of diphenyl dust per liter of air showed evidence of some respiratory difficulty which was not observed in rats treated at the same time in exactly the same manner.

No cases of chronic diphenyl or Dowtherm A intoxication in man have been reported in the published literature. Dowtherm A has been used extensively in industry as a heat-transfer medium for over 30 years.

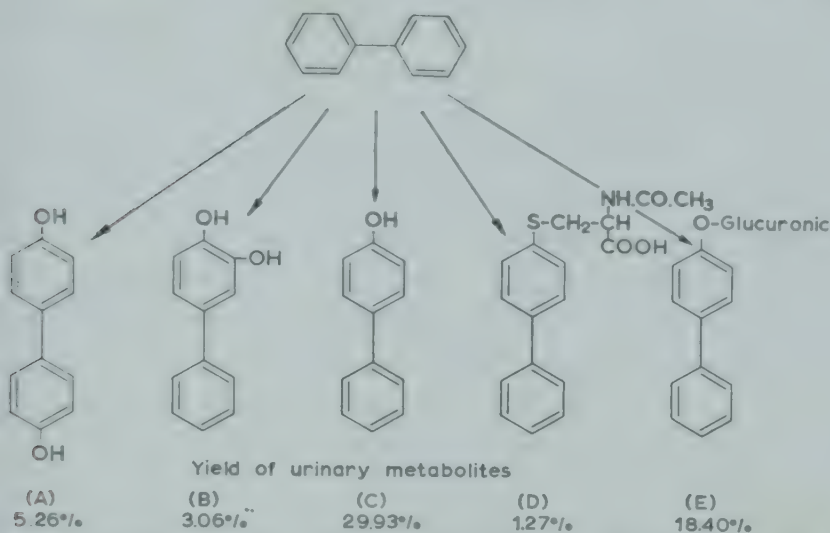
Biochemistry

Diphenyl is absorbed into the blood from the gastrointestinal tract, after topical application to the intact skin, and probably also by inhalation of hydrocarbon dust. Based on animal studies, it appears that systemic intoxication can result from repeated skin application of large amounts of diphenyl. After absorption into the blood, diphenyl is converted, presumably by the liver, into water-soluble hydroxyl derivatives. The results of a metabolic balance study conducted by West *et al.* (1956) with diphenyl in the rat are summarized in Fig. 68. None of the hydrocarbon is excreted unchanged in the urine or exhaled through the lung.

According to West *et al.* (1956) 4-hydroxydiphenyl conjugated with sulfuric acid has also been identified in the urine of the dog after oral dosing with the hydrocarbon. The su

aneous injection of diphenyl in rats causes a marked increase in urinary ethereal sulfate (Table 22, p. 76).

The administration of lethal and sub-lethal doses of diphenyl to rabbits resulted in moderate increases in hexuronates (ex-



88. Biotransformation of diphenyl in the albino rat (1% fed in the diet). (A) 4,4'-Dihydroxydiphenyl; (B) 3,4-Dihydroxydiphenyl; (C) 4-Hydroxydiphenyl; (D) Diphenylmercapturic acid; (E) Diphenylglucuronide.

(West, H. D. *et al.* (1956)).

sed in terms of glucuronic acid) and organic sulfates. Rabbits exposed repeatedly to the dust of diphenyl in concentrations approximating 0.04 mg per liter of air showed a normal urinary output of hexuronates and ethereal sulfates (Deichman, W. B. *et al.*, 1947).

Rats fed 1% diphenyl in the diet excrete a sulfur-containing metabolite in the urine which is believed to be a mercapturic acid. These rats did not grow at a normal rate unless the diet was supplemented with sulfur in the form of the amino acids cysteine or DL-methionine (West, D. and Jefferson, N. C., 1956).

Threshold limit

The threshold limit or maximum allowable concentration (MAC) for diphenyl has not been established. Based on results of animal experimentation, the maximum safe concentration of diphenyl in air for prolonged exposure for rabbits is above 0.3 mg per liter. The value for rats is between 0.01 and 0.04 mg per liter, and for mice it is below 0.005 mg per liter. According to Deichmann, W. B. *et al.* (1947), concentration of 0.005 mg per liter (0.75 p.p.m.) should be considered dangerous for prolonged human exposure. A threshold limit of 2 mg per m³ of air has been suggested for 'Dowtherm A' by the Imperial Chemicals Industry, Industrial Products and Health Research Committee (Table 24, p. 84). This is equal to 0.5 mg of diphenyl and 1.5 mg of diphenyl oxide.

Prevention, detection and treatment of exposure

(A) Prevention

Chemists, technicians and individual workers handling relatively small quantities of diphenyl should exercise care to avoid inhaling diphenyl dust or excessive, unnecessary skin contact with the solid hydrocarbon.

In the industrial plant processing large quantities of diphenyl engineering controls and industrial hygiene methods should be employed to maintain the concentration of diphenyl in the atmosphere at a level which is safe for repeated daily exposure. A threshold limit of 0.5 mg per m³ of air has been suggested. Workers exposed to excessive concentrations of diphenyl should be provided with suitable protective equipment such as face masks, goggles, gloves and protective garments depending on the nature of the work and the type of exposure.

(B) Detection

There is no established test to indicate that exposure to diphenyl dust has occurred or that diphenyl has been absorbed in sufficient quantity to cause sub-clinical or latent systemic intoxication.

on. A test for exposure could be based on the total quantity or concentration of hydrocarbon or metabolites of diphenyl in the urine. Another possibility is the use of the urinary sulfate since an increased urinary ethereal sulfate excretion was observed in rats after the subcutaneous administration of diphenyl (Table 22, p. 76).

Caution indicates that employees working with diphenyl should have regular periodic health examinations which include brief interval medical history, physical examination and complete blood count. The physician should direct his attention to symptoms and signs of mucous membrane, respiratory tract, and eye irritation. The absence of these premonitory symptoms of local irritation precludes the possibility of systemic intoxication due to inhalation of diphenyl. Although systemic intoxication was observed in animals dosed percutaneously with the quantities of diphenyl it is inconceivable that comparable exposures could exist or would be tolerated today in industry.

Treatment

The treatment of acute or chronic irritation of the eyes, mucous membranes of the respiratory tract and or skin consists in removing the individual from further exposure to diphenyl. Response in normal individuals is spontaneous amelioration and complete recovery.

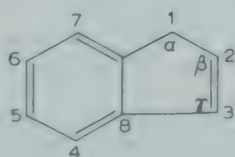
INDENE

Synonyms

Indonaphthene.

Molecular formula: C_9H_8 .

Structural formula:



Molecular weight: 116.15.

Physical properties

A water-white liquid having a pungent odor which readily polymerizes and oxidizes on standing (see further table on pp. 202 and 203).

Sources, uses and probable modes of contact

Indene is present in tars from coal, lignite, and crude petroleum. Newly developed processes have made commercial production possible. It has not been available in commercial quantities until recently because of the high cost of isolating it from coal tar or cracked petroleum fractions in which limited quantities are found.

The principal use of indene has been in the production of coumarone-indene resins manufactured by polymerizing coumarone and indene in a coal tar fraction. Indene is also a minor constituent of coal tar naphtha insecticides. The commercial hydrocarbon of high purity (98 %) serves as a starting material for synthesis of plastics, elastomers, polyester fibers, plasticizers and drugs.

The most likely modes of contact with indene in its present industrial applications are inhalation of vapor or mist and cutaneous contact with the liquid hydrocarbon.

Analytical methods

Indene undergoes the general reactions of the mono-aromatic hydrocarbons. It absorbs strongly in the ultra-violet and infrared. It can also be nitrated and it reacts with the sulfuric acid-formaldehyde reagent to form colored compounds. These general reactions may be adapted for the qualitative and quantitative analysis of indene in the atmosphere and in biological fluids (see Chapter 3).

Toxicology

A limited number of toxicological studies have been conducted on indene.

Based on analogy between chemical constitution and the known toxicological effects of mono-aromatic hydrocarbons, the inhalation of indene vapors and mists can be expected to cause irritation of mucous membranes. The intensity of the effect depends on the concentration of the hydrocarbon and the duration of the exposure. Quantitative vapor inhalation studies on human subjects have not been described in the published literature.

Liquid indene on prolonged or repeated contact with the skin removes the natural tissue fats which may lead to dermatitis. The aspiration of liquid indene directly into the lung causes chemical pneumonitis, pulmonary edema and hemorrhage in experimental animals (Gerarde, H. W., unpublished observations).

The mammalian toxicity of indene was investigated by Cameron and Doniger (1939) who were concerned with the presence of the hydrocarbon in coal tar naphtha insecticide solvents. No local cutaneous or general systemic effects developed after painting the shaved and unshaved skin of rats 1 to 8 times with 0.1 ml of undiluted indene. Guinea pigs were also unaffected by 3 applications of 0.5 ml of undiluted indene to the shaved skin.

Cameron and Doniger also reported that rats weighing 180-200 g survived the repeated subcutaneous injection of unstated amounts of the undiluted hydrocarbon. Fatty livers and fatalities resulted when 1.0 g of indene was injected subcutaneously in rats.

Böhm (1941) found that rabbits weighing 2-3 kg tolerated 1.0 g of indene administered orally with no evidence of systemic intoxication.

The mortality ratio in male albino rats weighing 200-250 g dosed orally with 2.5 ml of a 1:1 v/v mixture of indene in olive oil was 10/10 (Table 13, p. 55). Post-mortem examination revealed a generalized vasodilatation, hyperemia and hemorrhage of the gastrointestinal tract, pulmonary edema and hemorrhage.

Histological examination showed a diffuse chemical hepatitis and the presence of hemoglobin crystals in the pulmonary alveolar capillaries (Fig. 69).

A dog with a bile fistula was dosed by gastric intubation v

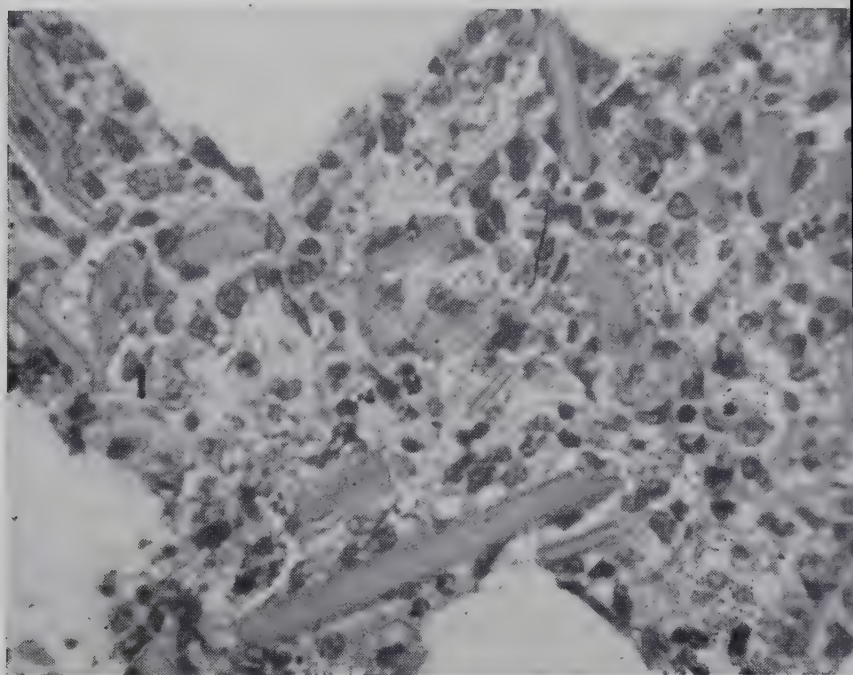


Fig. 69. Deposition of hemoglobin crystals in pulmonary alveolar capillaries of rat after a single oral dose of indene. (Gerarde, H. W., 1930)

5 ml of indene daily for 5 days to study the effect of the hydrocarbon on bile production (Smith, H. P. and Whipple, G. 1930). Considerable retching and vomiting was observed after the administration of each dose of indene. In spite of this, the animal was able to eat and maintained its body weight during the dosing period. Indene was found to have a powerful choleretic effect equivalent in potency to cholic acid.

There were no deaths in a group of 20 rats that received 7½ hour exposures to indene vapors at a concentration of 0.08-0.09% v/v (approximately 800-900 p.p.m.) (Cameron)

R. and Doniger, C. R., 1939). Liver damage and occasionally splenic and renal injury were found in the exposed animals. The liver histopathology varied from slight fatty degeneration to severe necrosis. Acute cytolytic necrosis (acute yellow atrophy) was found in the livers of the young animals exposed to indene vapor. The liver necrosis was zoned in distribution, affecting primarily the central zone around the intralobular vein. Hemorrhages were occasionally seen, chiefly around the central vein. Histological abnormalities found in the kidney consisted of wedge-shaped focal necrosis which resembled tiny infarcts. Complete blood examinations of the animals exposed to indene vapors showed no significant deviations from normal. The adrenal, pancreas, pituitary, ovary and testis were also normal on microscopic examination.

biochemistry

Indene is absorbed by inhalation of vapor or mist, from the gastrointestinal tract after oral dosing and probably very slowly through the intact skin. After absorption, it is converted by the liver to water-soluble metabolites which are conjugated with sulfate and glucuronic acid and excreted as urinary metabolites. Smith and Whipple (1930) concluded from their studies that the dog cannot utilize indene to synthesize cholic acid, which contains 2 indene rings.

Böhm (1941) reported that the administration of indene to rabbits was followed by an increased excretion of ethereal sulfate and glucuronide which is evidence that indene undergoes hydroxylation in the animal body. The subcutaneous injection of indene in rats causes a marked increase in urinary ethereal sulfate excretion. See Table 22, p. 76.

Brooks and Young (1956) found that 5% of the dose of indene administered to rabbits by stomach tube could be isolated from the urine as optically active *cis*- and *trans*-indane-1,2-diol. Acid treatment of the urine, either before or after ether extraction, yielded indan-2-one in amounts corresponding to 25%

of the dose of indene administered orally. The ketone and from conjugates of the diols with glucuronic acid or sulfuric acid. An increased glucuronide excretion was observed in rabbits after dosing with indene (0.5 g/kg body weight). The same 2 diols were also isolated from the urine of rabbits dosed with indene by subcutaneous injection.

The biotransformations in indene occur at the double bond in the 5-membered ring which is hydroxylated. The benzene ring remains unchanged. There is no evidence that epoxide formation occurs in the animal body during the metabolism of indene.

The biochemical conversions of indene in the rabbit are shown in Fig. 70.

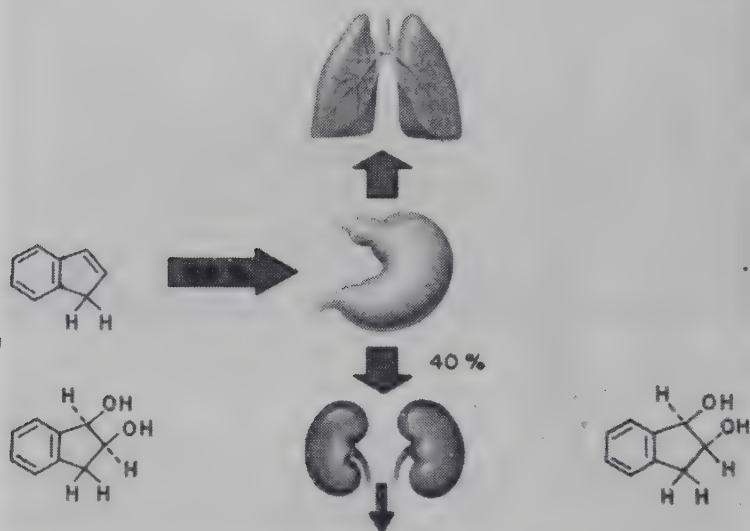


Fig. 70. Elimination and biotransformation of indene in the rabbit in 72-hour interval after a single oral dose. Principal urinary metabolites left to right: *cis*-indane-1,2-diol and *trans*-indane-1,2-diol.

(Brooks, C. J. W. and Young, L., 19

Threshold limit

The maximum allowable concentration (MAC) for indene in the working atmosphere for an 8-hour workday has not been established.

Prevention, detection and treatment of exposure

1) Prevention

The chemist, technician or worker using relatively small quantities of liquid indene should take the usual precautions to avoid unnecessary exposure to the vapors and skin contact with the liquid hydrocarbon.

In the industrial plant in which large quantities of indene are used, engineering controls and industrial hygiene methods could be employed to maintain the atmospheric concentration at a safe level for repeated daily exposure. Based on the toxicological studies conducted with indene and analogy with hydrocarbons for which threshold limits have been established a value of approximately 50 p.p.m. appears to be reasonable. The toxicological studies conducted are not adequate to suggest more than an approximate maximum allowable concentration. Workers who are unavoidably exposed to excessive vapor concentrations of indene or who are apt to have skin contact with the liquid should be provided with suitable respiratory equipment and protective garments.

2) Detection

There is no established biochemical test which indicates that exposure to indene vapor has occurred or that sufficient indene vapor has been absorbed under actual working conditions to cause sub-clinical or incipient toxicity. Indene causes a marked elevation of the urinary sulfate ratio in rats dosed subcutaneously with the hydrocarbon. This change in urinary sulfate ratio may possibly serve as an index of human exposure to indene under working conditions. The urinary sulfate ratio is used as a test for exposure to benzene under actual working conditions (Chapter 7). The detection in the urine of the specific metabolites of indene shown in Fig. 70, also has possibilities for developing into a practical test for exposure to indene. Considerable clinical study is required before the validity of such a test can be established.

Periodic health examinations should be conducted at regular intervals on workers who may have exposure to indene. Each medical examination should include a brief interval medical history, physical examination and complete blood count. During the medical history and the physical examination, particular attention should be directed by the physician to symptoms and signs indicative of mucous membrane, eye and skin irritation. It is highly improbable that systemic intoxication due to dermal sorption of indene would be found in the absence of the premonitory signs and symptoms of local irritation. Complaints of eye, nose or respiratory tract irritation are justification for investigating the individuals working conditions.

(C) Treatment

Indene has a low vapor pressure at room temperature (1.7 mm Hg at 25°) so that there is little hazard of accumulating vapor in the air due to spontaneous evaporation of the hydrocarbon. Acute intoxication by indene vapor inhalation is possible under special conditions such as working in a confined space or accidental spilling of indene at an elevated temperature. The treatment of acute poisoning by inhalation of vapors of aromatic hydrocarbons is described in detail in Chapter 6, p. 10.

The symptoms and signs of chronic indene over-exposure (skin, eye, respiratory tract irritation) respond favorably to removal of the affected individual from further exposure to the hydrocarbon.

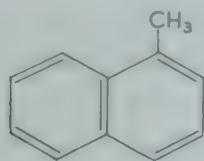
For further general discussion of the treatment of aromatic hydrocarbon intoxication see Chapter 6.

1- AND 2-METHYLNAPHTHALENE

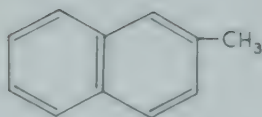
Synonyms

α - and β -Methylnaphthalene.

Molecular formula: $C_{11}H_{10}$.

Structural formulas:

1-methylnaphthalene or
 α -methylnaphthalene



2-methylnaphthalene or
 β -methylnaphthalene

Molecular weight: 142.19.

Physical properties

(See also table on pp. 202, 203.)

Vapor pressure:

100 mm Hg

30 mm Hg

10 mm Hg

1 mm Hg

Temperature °C:

α

β

167.78

164.68

133.6

130.7

107.4

104.7

63.5

61.1

Surface tension: dynes/cm 20°

40.68

38.44

sources, uses and probable modes of contact

1- and 2-Methylnaphthalene occur in coal tar and in petroleum from various parts of the world. 2-Methylnaphthalene is reported to be predominant among the naphthalene derivatives in Trinidad petroleum. The hydrocarbon isomers are found in the coal-tar fractions boiling at 230-248° and may be separated from one another by a number of chemical and physical procedures. Some of these are: (1) isolation and decomposition of the isomers, (2) freezing out the 2-methyl isomer at -20 to -30°, (3) sulfonation of the mixture with concentrated sulfuric acid at -10 to -20° and preferential desulfonation, (4) alkylation with a tertiary olefin followed by distillation or crystallization and dealkylation, and (5) fractional distillation. The isomers can also be synthesized from suitable chemical precursors. Commercial mixtures of the mono-methylnaphthalenes are extensively used as insect toxicant solvents in formulations with

synthetic insecticides such as DDT, methoxychlor and benz hexachloride.

1-Methylnaphthalene is used as a primary reference fuel for the standardization of diesel engine fuels, as a constituent of heating-bath oils and as a starting material for synthesis of *alpha* naphthoic acid.

2-Methylnaphthalene is used as a constituent of heating-bath oils and as a starting material for synthesis of Vitamin K, d and other chemicals. It has also been used as a potato sprout inhibitor.

The most likely modes of contact with the mono-methylnaphthalenes in the industrial applications described are direct skin contact with liquid 1-methylnaphthalene or the solid 2-methylnaphthalene and possible inhalation of dusts, mists, aerosols or vapors of either.

Analytical methods

The general physical and chemical methods described for the analysis of the aromatic hydrocarbons in Chapter 3 can be adapted for the analysis of the mono-methylnaphthalenes in air and in biological fluids and tissues. Concentration and separation of the hydrocarbons from the sample source are necessary preliminary steps before the analysis can be undertaken. 1- and 2-Methylnaphthalene form addition complexes such as picrates and styphnates, which may serve for isolation, identification and quantitative analysis.

Toxicology

The direct application of 1- and 2-methylnaphthalene to the skin of the ulnar aspect of the forearm exposed to direct solar radiation did not cause tingling, prickling or erythema (Gerard H. W., unpublished observations). The pure mono-methylnaphthalenes on single topical application (without confinement of the hydrocarbon under a patch test) are not primary skin irritants or photosensitizers. Extensive tests have been conducted

h refined commercial solvent mixtures consisting primarily the mono-methylated naphthalenes (Draize, J. H. *et al.*, 1946). Continuous cutaneous contact with the solvent for 48 hours under a patch test caused negative to slight skin reactions in 4 out of 5 human subjects tested. One subject was graded as having a 'moderate' reaction after 24 hours of contact under the patch test. In 3 additional subjects tested, the patch test was removed because of irritation 1 hour after application. Each of these showed some evidence of irritation upon removal of the test, but the reaction did not persist probably because of the short period of exposure. It was concluded that this commercial mono-methylated naphthalene solvent mixture was less irritating than kerosine which was used for comparison in these primary skin irritation studies. The commercial mixture of 1- and 2-methylnaphthalene did not cause cutaneous photosensitization in the human subjects tested.

The cutaneous toxicity of the commercial solvent mixture of mono-methylated naphthalenes in experimental animals was

TABLE 40

SUBACUTE DERMAL TOXICITY OF
MONO-METHYLATED NAPHTHALENE MIXTURE IN RABBITS*

<i>Dose: ml/kg</i>	<i>Mortality ratio</i>	<i>Remarks</i>
4.0	2/2	Deaths occurred after 6 and 7th dose. Anorexia after first dose. Severe irritation and necrosis of skin.
2.0	1/2	Death occurred after 8 doses. Second rabbit survived 21-day experiment. Severe skin irritation.
1.0	0/2	Moderate weight loss. Anorexia after first dose persisted to end of experiment (21 days). Severe irritation and sloughing of skin.

*after Draize, J. H. *et al.* (1946).

also tested by Draize *et al.* The results of the repeated application of the solvent to the intact skin of rabbits at various levels are summarized in Table 40.

One rabbit was sacrificed after skin exposure to 2.0 ml/kg for 9 days. The results of the gross and microscopic tissue changes found in this animal are summarized in Table 41.

TABLE 41

PATHOLOGICAL CHANGES IN RABBIT FOLLOWING REPEATED SKIN EXPOSURE TO MONO-METHYLATED NAPHTHALENE SOLVENT MIXTURE

<i>Tissue</i>	<i>Remarks</i>
Skin	Thin, red, scaly
Liver	Tan color, necrotic foci. Fatty degeneration
Stomach	Dark fluid
Heart	Myocarditis, fibrosis
Bone marrow	Hyperplastic. Increase in erythroid elements
Spleen	Hyalinization of follicles
Thigh muscle	Focal necrosis
Thyroid epithelium	Lower than normal
Gall bladder, brain, pancreas, adrenal, parathyroid	Normal

* After Draize, J. H. *et al.* (1946).

Another rabbit survived the repeated inunction with 2.0 ml of the mono-methylated solvent mixture for 21 days. Post-mortem examination showed that visceral pathology was limited to moderate hyperplasia of the bone marrow and the thyroid gland. The heart, liver, gall bladder, spleen, lymph nodes, pancreas, kidney, adrenal, parathyroid, voluntary muscle and brain were 'negative' or essentially normal.

Svirbely *et al.* (1946) investigated the inhalation toxicity of aerosols or mists of the mono-methylated naphthalene solv-

mixture in experimental animals. Dogs, rats, rabbits, guinea pigs and mice received 27 daily one-hour exposures to the methylated naphthalene solvent mist at a concentration of 16.02 mg/liter during a 35 day experimental period. The median size of the mist droplets was 3.15μ . A rough idea of the concentration of the mist used may be gained from the fact that the 'visibility' in the exposure chamber was approximately 10 feet.

The effects of exposures to the mist observed in the animals were the following: (1) Dyspnea, listlessness, prostration, irritation of the eyes and redness of the ears in the mice after the second exposure of 1 hour, (2) After 4 hours of exposure, marked salivation in the dogs, and redness of the ears in the rats and

TABLE 42
MORTALITY IN ANIMALS EXPOSED TO
MIST OF MONO-METHYLATED NAPHTHALENE MIXTURE*
(27 one-hour exposures, 16.02 mg/l)

No. of animals	Incidence of death						No. Animals surviving
	0	5	10	15	20	25	
3							3
3							3
15							15
6							5
6							6
20							12
	×	×					
	×	×	×	×			
	×	×					
	0	5	10	15	20	25	
	Days of exposure						

* Death of single animal during or following the exposure indicated.
After Svrbely, J. L. *et al.* (1946).

rabbits, (3) Dyspnea was observed in the guinea pigs after exposure, (4) Slight weight loss in mice but normal weight in the other animals.

The mortality during the experimental period is shown in Table 42.

Hematological examination showed no significant deviation from normal in erythrocytes, hemoglobin, hematocrit, reticulocytes, total or differential leukocyte counts. The bromsulphalein liver retention tests performed weekly on the dogs were essentially normal.

Histological examination of tissues of animals sacrificed at the termination of the experiment revealed that the pathological changes were primarily in the lung, liver and skin. Pulmonary changes consisted of bronchopneumonia, thickening of parabrachial alveolar septa, edema and emphysema. A slight hyperkeratosis of the epithelium of the skin of the ears was found in the rabbits and moderate deposition of fat in the hepatic cords.

Fitzhugh and Buschke (1949) fed rats 2% 2-methylnaphthalene incorporated in the diet for 2 months. No tumors or preneoplastic changes were found in these animals at the end of the experiment.

Biochemistry

The metabolism of 2-methylnaphthalene in the rabbit, guinea pig and mouse was investigated by Grimes and Yocum (1956). After oral dosing, the urine of the dosed animals contained a variety of metabolites of the hydrocarbon which were identified by paper chromatography. 2-Naphthoic acid was identified in the urine of the 4 animal species indicating that the methyl group is oxidized to the carboxyl group. This conversion is comparable to the *in vivo* transformation of toluene to benzoic acid.

2-Methylnaphthalene also undergoes hydroxylation in the animal species tested since the urine showed the presence of 7-methyl-1-naphthol and 7-methyl-2-naphthol. This is analogous to the conversion of naphthalene in these animal species. 1,2-dihydrodiol was also identified which is believed to be

1,2-dihydro-7-methyl-naphthalene-1,2-diol. This is the first reported instance of a methyl substituted hydrocarbon which is transformed *in vivo* to a dihydrodiol.

The biotransformations of 2-methylnaphthalene in the rat, rabbit, mouse and guinea pig are shown in Fig. 71.

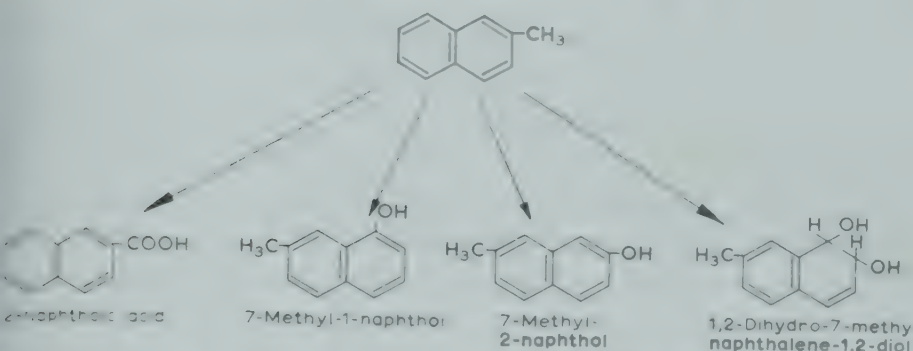


Fig. 71. Biotransformations of 2-methylnaphthalene in the rat, mouse, rabbit and guinea pig. (Grimes, A. J. and Young, L., 1956).

Threshold limit

The maximum allowable concentration (MAC) of 1- and 2-methylnaphthalene in the atmosphere for an 8-hour workday has not been established.

Prevention, detection and treatment of exposure

4) Prevention

Unnecessary exposure to the vapors, mists containing the hydrocarbon or contact with the liquid should be avoided. The industrial plant using the hydrocarbon in large quantities should be equipped with engineering controls and employ industrial hygiene methods designed to maintain the concentration in the air at a safe level for repeated daily exposure. Although the threshold limit has not been established for the mono-methylnaphthalenes, some approximation can be made based on the toxicological studies reported and analogy with hydrocarbons of similar chemical constitution for which values have been established. A threshold limit of about 25 p.p.m. appears to be

reasonable and is suggested as a tentative figure. Additional details for the safe handling of volatile hydrocarbons under special circumstances where excessive exposure may occur are presented in Chapter 9 (Xylene).

(B) Detection

A sensitive test has not been established to indicate whether exposure to mono-methylnaphthalene vapors or mists has occurred or if the absorption of the hydrocarbon has caused a biochemical abnormality indicative of sub-clinical intoxication. The detection of specific metabolites of the hydrocarbon in the urine might be the basis for an exposure test for the mono-methylnaphthalenes. Another possibility is the urinary sulfonate ratio which was found to be decreased in rats injected subcutaneously with the hydrocarbon (Gerarde, H. W., unpublished observation).

Caution indicates that periodic health examinations should be conducted on workers who may be exposed to the mono-methylnaphthalenes. The health inventory should include a brief interval medical history, physical examination and a desired complete blood count. The physician should direct attention to symptoms and signs indicative of local mucous membrane irritation of the nose, respiratory tract, the eyes and skin. In the absence of premonitory evidence of local irritation it is hard to imagine that systemic intoxication could possibly exist in workers exposed to the monomethylnaphthalenes.

(C) Treatment

The low vapor pressure of the mono-methylnaphthalenes (1 mm of Hg at 63.5°) at room temperature makes it highly improbable that acute intoxication due to vapor inhalation of the hydrocarbon could occur except under most unusual circumstances. The first aid treatment and medical management of acute poisoning by inhalation of vapors of the volatile aromatic hydrocarbons is discussed in detail in Chapter 6, p. 9.

The local irritation of the eyes, mucous membranes of the respiratory tract and or skin which may be found as a result of repeated over-exposure to the mono-methylnaphthalenes responds favorably to 'tincture of time' after removing the individual from further contact with the hydrocarbon.

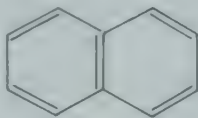
NAPHTHALENE

Synonyms

Naphthalin, naphthene, tar camphor, 'moth balls', white tar.

Molecular formula: $C_{10}H_8$.

Structural formula:



Molecular weight: 128.16.

Physical properties

A white solid having the odor of 'moth balls' (see further table on pp. 202 and 203).

Sources, uses and probable modes of contact

Naphthalene is obtained by crystallization from the middle or 'carbolic oil' fraction of distilled coal tar. Coal tar contains about 11% naphthalene which makes it the most abundant single constituent in this complex chemical mixture. It is purified by hot pressing followed by washing and distillation or sublimation. Naphthalene is also present in streams from catalytic cracking processes. If coke ovens cannot meet the demand for naphthalene, petroleum may become a source of this hydrocarbon.

Naphthalene is sold in the form of scales, powder, and the familiar 'moth balls' which are widely used as a moth repellent. It is also used extensively as a source of phthalic acid and antranilic acid which are employed as intermediates in the synthesis of dyes and numerous other chemicals. Liquid hydro-

generated derivatives of naphthalene 1,2,3,4-tetrahydride (tetralin) and the decahydride (decalin) are used in motor fuels, lubricants, and solvents. Naphthalene has also been used in medicine as an intestinal antiseptic and anthelmintic, and as a dust powder in skin diseases. Fumigations have also been tried for the treatment of pertussis.

Although naphthalene is a solid, it volatilizes appreciably at room temperature so that inhalation of vapors or fumes is one of the most probable modes of contact in the present commercial uses of the hydrocarbon. In addition, the fumes may deposit on the skin surface or direct skin contact with the solid hydrocarbon may occur in handling the chemical.

Analytical methods

Naphthalene vapor in the atmosphere may be determined with the interferometer or spectrometer, by means of chemical analysis based on the formation of the hydrocarbon picrate or by colored nitro derivatives, or gravimetrically. In the latter procedure the hydrocarbon is collected by condensation at low temperatures or absorbed on charcoal or silica gel. These methods may also be used for the estimation of naphthalene in biological materials (urine, blood and tissues) after conducting a preliminary step to separate the hydrocarbon from the original sample.

Toxicology

(A) Animal studies

Cataracts resembling human senile cataracts have been produced in rabbits by the repeated oral administration of naphthalene (Adams, D. R., 1930). Lens changes appear within 1 to 3 days after dosing orally with 1 g per kg of body weight. The lesion progresses so that the lens becomes completely opaque in about 20 days. Cataracts are also produced in rats by dosing with naphthalene (Fig. 72). A 5-kg dog dosed orally with 1 to 5 g of naphthalene daily for 16 days became extremely emaciated.

and developed a hemorrhagic nephritis and a decrease in hemoglobin and erythrocyte count (Meyer, S., 1920). The animal made complete recovery three weeks after the administration of the last dose of naphthalene. In another study with dogs fed naph-

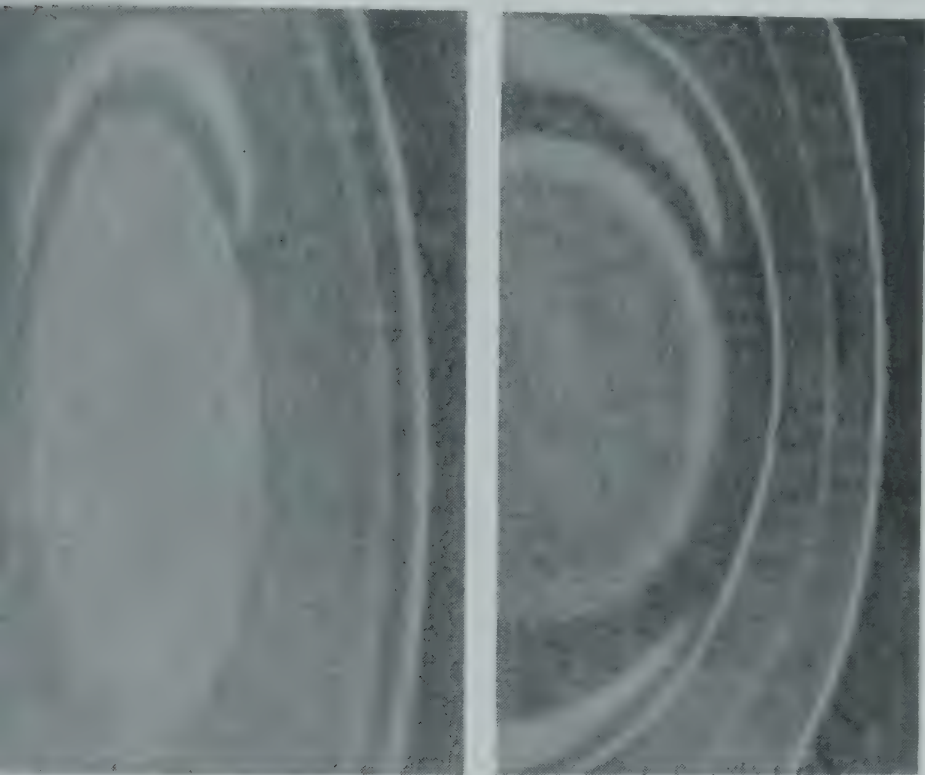


Fig. 72. Cataractogenic activity of naphthalene in rats. Optical sections of anterior segment of eye. Left: Appearance of lens on 7th day after 4 daily doses of 0.1 g of naphthalene; right: Appearance of lens on 48th day after daily doses of 0.18g (5 weeks later). (Goldmann, H., 1929).

thalene, the animals developed acute hemolytic anemia and hemoglobinuria but made a rapid, complete recovery after dosing with naphthalene was discontinued (Zuelzer, W. M. and Apt, L., 1949).

3) Human experience

Naphthalene is a primary skin irritant. Some individuals are

hypersensitive to naphthalene and develop a dermatitis relatively slight skin contact. A severe generalized erythema reported in an individual who handled clothes sprinkled naphthalene moth repellent (White, R. P., 1934). A moist matitis of the hands, forearms, neck, abdomen and thighs reported in workers handling mineral oil containing from 1.5% naphthalene. These lesions cleared up rapidly when contact with naphthalene was discontinued (Eisner, E., 1924).

Naphthalene vapors may cause eye irritation, headache, nausea and profuse perspiration, depending on the concentration of the hydrocarbon in the air and the duration of the exposure to this atmosphere. Vomiting, optic neuritis, hematoma and edema have been reported in individuals exposed to atmospheric concentrations of naphthalene fumes or vapors. Ghetti and Mariani (1956) have found lens opacities in 8 of 21 employees exposed to high concentrations of naphthalene fumes or vapors for a five year period. Only 1 of the 8 individuals was over 50 years of age and 2 out of 4 in the 20-30 year group had lenticular opacity. The lesions were in the peripheral part of the lens and were unlike the cataracts found in glass blowers or foundry workers.

Naphthalene was used therapeutically for many years as an antiseptic and anthelmintic. It was particularly effective in the treatment of pinworm. The recommended oral dose for adults ranged from 0.1 to 0.5 g, and for children 0.05 g to 0.1 g taken three times daily. Two g of naphthalene administered orally over a 2-day period caused the death of a 6 year old child (Sollmann, T., 1957). The probable lethal oral dose for an adult is 5-15 g. The ingestion of an over-dose of naphthalene causes nausea, vomiting, abdominal pain, irritation of the bladder, and the urine is colored brown or black. The symptoms of intoxication usually disappear in a few days. Hemolytic anemia has been reported in children following the accidental ingestion of naphthalene 'moth balls'. It has been reported that a child was believed to have ingested naphthalene for a period of

ear before developing signs and symptoms of intoxication (Pfizer Spectrum, 1958).

Fifty cases of severe intoxication following the repeated ingestion of a naphthalene-isopropyl alcohol 'cocktail' have been described (Gadsden, R. H. *et al.*, 1958). The 'beverage of voltage rather than vintage', called 'scrap-iron' because of its metallic taste, caused an acute intoxication identical with the delirium tremens produced by ethyl alcohol. The symptoms consisting of tremor, restlessness, extreme apprehension and hallucinations subsided in a few days.

Examination of the peripheral blood in naphthalene intoxication shows evidence of erythrocyte fragmentation, Heinz bodies in the red blood cells, eccentrically concentrated hemoglobin in the erythrocytes, hypochromia and polynucleosis. The bone marrow may appear hyperplastic and show an increased proportion of nucleated cells of the erythrocyte series.

Biochemistry

Naphthalene is absorbed into the blood by inhalation of vapors or fumes of the hydrocarbon. It is absorbed very slowly from the gastrointestinal tract. No information has been found in the published literature regarding the tendency or ability of naphthalene to penetrate the intact skin.

Naphthalene itself is non-hemolytic *in vivo* or *in vitro*. It is converted, presumably in the liver, to a number of metabolites which may be hemolytic *in vitro* and or *in vivo*. Chemical and spectro-photometric examination of the urine in cases of human naphthalene intoxication has revealed the presence of α -naphthol, β -naphthol, α -naphthoquinone and β -naphthoquinone. These naphthalene metabolites are hemolytic agents. According to Mackell *et al.* (1951) the hemolytic activity of the naphthalene metabolites decreases in the following order: α -naphthol, β -naphthol, α -naphthoquinone and β -naphthoquinone.

It appears that susceptibility to naphthalene hemolytic anemia

may be restricted to certain individuals, particularly negroes, in whom an abnormality of glutathione metabolism exists (Ham, W. H., and Childs, B., 1958). This characteristic is genetically determined and accordingly is an 'inborn error of metabolism'. Newborn infants appear to be particularly susceptible to naphthalene. This is believed to be due to metabolic immaturity rather than genetic abnormality of the erythrocytes.

The biotransformation products of naphthalene in the rat are shown in Fig. 73.

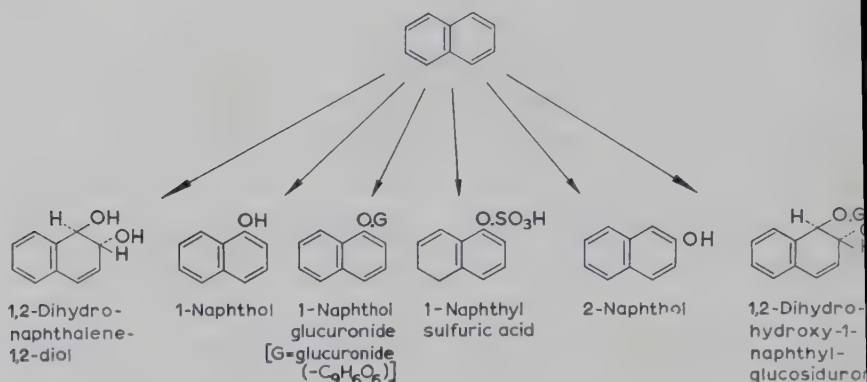


Fig. 73. Principal urinary metabolites in biotransformation products of naphthalene in the rat. G = Glucuronide ($-\text{C}_9\text{H}_6\text{O}_6$).

(Corner, E. D. S. and Young, W. H., 1958)

Threshold limit

The threshold limit for naphthalene in the atmosphere for an 8-hour working day has not been established. Based on toxicological studies conducted with animals and human experience with naphthalene a concentration of 25 p.p.m. appears to be a reasonable level. This figure is approximately 25 times the concentration of naphthalene vapor in saturated air at 25°C.

Prevention, detection and treatment of exposure

(A) Prevention

Workers handling naphthalene should be protected against inhalation of naphthalene vapor, dust or fume by supplying them with appropriate respiratory protection.

em with suitable protective equipment. Skin contact should be avoided and goggles should be worn to protect the eyes. Engineering controls and if necessary, general and local exhaust ventilation should be used in the plant to maintain the air concentration below the suggested threshold limit of 25 p.p.m.

3) Detection

There is no established test which indicates that exposure to naphthalene vapor has occurred or that sufficient naphthalene has been absorbed under actual working conditions to cause sub-clinical or incipient toxicity. In human cases of acute naphthalene intoxication due to ingestion of the hydrocarbon, chemical and spectrophotometric examination have shown the presence of naphthols and naphthoquinones in the urine. The detection and quantitative analysis of these metabolites may form the basis for a test for chronic exposure to low atmospheric concentrations of naphthalene. Clinical studies must be conducted to prove the validity of the test under actual working conditions. The concentration or total 24-hour urinary output of these metabolites may serve as indices of exposure after these values are correlated with the air concentration and duration of exposure to this atmosphere. If a sufficiently sensitive specific method were available for the analysis of the hydrocarbon itself, the amount of naphthalene in the urine could also be used as a measure of exposure to the hydrocarbon.

Periodic health examinations should be conducted at regular intervals on workers who are exposed to naphthalene. The medical examination should include a brief interval history, physical examination and complete blood count. Attention should be directed by the physician to symptoms and signs of local irritation of the eyes, mucous membranes and skin. In the absence of symptoms or evidence of local irritation of mucous membranes, systemic intoxication due to absorption of naphthalene is highly improbable. Because of the cataracts reported in employees exposed to high concentrations of naph-

thalene fumes, vapors or dusts, a thorough examination of the eye should be included in the physical examination.

(C) Treatment

Because of the low vapor pressure of naphthalene at room temperature acute intoxication due to inhalation is not likely to occur except under unusual circumstances which would permit high concentrations of vapor to accumulate. The first aid treatment and medical management of acute intoxication from vapor inhalation is described in detail in Chapter 6.

Mucous membrane and skin reactions due to contact with naphthalene respond favorably in normal individuals to removal from further contact with the hydrocarbon. Individuals who are sensitized or hypersusceptible to naphthalene should be removed permanently from any type of work in which contact with the hydrocarbon is apt to occur. Sensitivity to naphthalene may be determined by careful patch testing.

The treatment of acute intoxication due to ingestion of naphthalene should include prompt emptying of the stomach by emesis and/or gastric lavage, followed by the administration of demulcents such as milk or egg white. Stimulants such as caffeine may be necessary. If sufficient naphthalene has been absorbed to cause hemolysis, hemoglobinuria and anemia, alkalization and blood transfusions may be indicated (Deichman, W. B., and Gerarde, H. W., 1958).

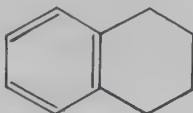
TETRALIN

Synonyms

Tetrahydronaphthalene, 1,2,3,4-tetrahydronaphthalene, tetralin, naphthalene 1,2,3,4-tetrahydride.

Molecular formula: $C_{10}H_{12}$.

Structural formula:



Molecular weight: 132.20.

Physical properties

A clear, colorless liquid with an odor resembling naphthalene (see further table on pp. 202 and 203).

Sources, uses and probable modes of contact

Tetralin is produced commercially by the partial catalytic hydrogenation of purified naphthalene.

It is used principally as a solvent for fats, waxes, resins, oils, asphalt and rubber, as a substitute for turpentine in lacquers, oil paints and shoe polish, and as a mosquito larvicide and vermifuge (Cuprex).

Contact with tetralin in its present commercial uses may occur by inhalation of vapors or mists and by skin contact with the liquid hydrocarbon.

Analytical methods

Tetralin in the atmosphere may be determined with field equipment such as the interferometer, combustion apparatus and the aromatic hydrocarbon detector calibrated for this hydrocarbon (see Chapter 3). Infrared, ultra-violet absorption, and colorimetric procedures (nitration and reaction with formaldehyde-sulfuric acid mixture) may also be used. The infrared, ultra-violet and visual colorimetric methods can be adapted for the determination of tetralin in biological fluids and tissues after separation of the hydrocarbon from the sample by extraction or distillation.

Toxicology

4) *Animal studies*

Liquid tetralin is a primary skin irritant which may cause erythema, drying and defatting of the skin. The intensity of the irritant reaction depends on the quantity of the liquid hydrocarbon in contact with the skin and the duration of the exposure. Eczematous dermatitis was produced in guinea pigs by the repeated application of liquid tetralin (Cardani, A., 1942).

Oettel found methemoglobin in the blood of cats dosed simultaneously with liquid tetralin (Lehmann, K. B. and Flury 1943). Direct contact of liquid tetralin with lung tissue (a) causes pulmonary edema and hemorrhage at the contact with the tissue (Gerarde, H. W., unpublished).

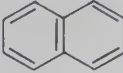
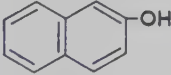
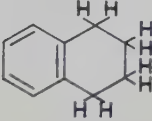
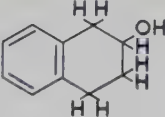
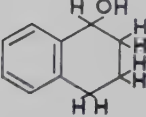

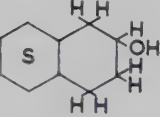
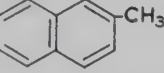
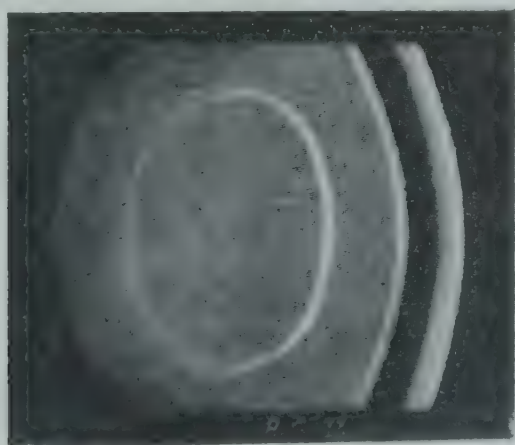
<u>CHEMICAL</u>	<u>FORMULA</u>	<u>POTENCY</u> (Naphthalene = 1)
Naphthalene		1
β -Naphthol		1
Tetrahydronaphthalene (Tetralin)		0
β -Tetralol		4
α -Tetralol		0
Decahydronaphthalene (Decalin)		0
<i>Trans</i> - β -decalol		0
β -Methylnaphthalene		0

Fig. 74. Cataractogenic potency of tetralin and tetralols compared with naphthalene derivatives and their metabolites (Weanling rats, 2% of chow in diet for at least 2 months).

(Fitzhugh, O. G. and Buschke, W. H., 1961).

tion). No adverse effects or evidence of injury were found in rabbits dosed once by mouth with 2.5-3 g of liquid tetralin per g of body weight (Pohl, J. and Rawicz, M., 1919). Higher doses caused diarrhea, narcosis and death. Rabbits fed 2 g of tetralin daily for 14 days developed oliguria and hematuria in the last few days of the experimental period (Rockemann, W., 1922). The following was observed in 8 guinea pigs dosed subcutaneously with 0.2 g of tetralin per day for 10 days: one animal died on the sixth day of the experiment, another died on the 9th day, the survivors appeared unthrifty, had lost considerable weight, and were restless and agitated. Examination of the peripheral blood showed a decrease in hemoglobin and the red blood cell count (from 5-6 million (normal) to 4 million per mm^3), monocytosis, lymphocytosis and neutropenia. Cataracts were found in rabbits dosed repeatedly (30-40 days) by the oral route with 0.2-1 ml of tetralin (Basile, G., 1939). Weanling rats fed a diet containing 2% tetralin for 2 months did not develop cataracts (Fitzhugh, O. G. and Buschke, W., 1949). β -Tetralol fed in the diet at the same concentration as tetralin for 2 months was found to be a potent cataractogen



75. Optical section of the anterior segment of the eye of a rat fed a diet containing 2% β -tetralol for two and one-half weeks.
(Fitzhugh, O. G. and Buschke, W. H., 1949).

for rats. The relative cataractogenic potency of naphthalene derivatives and their metabolites according to Fitzhugh and Buschke is shown in Fig. 74. Figs. 75 and 76 show the appearance of the cataracts found in the rats

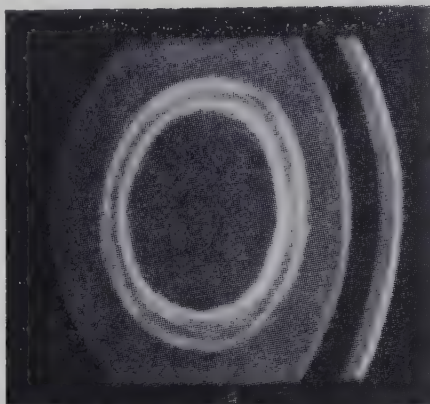


Fig. 76. Optical section of the anterior segment of the eye of a rat fed a diet containing 2% β -tetralol for three and one-half months.

(Fitzhugh, O. G. and Buschke, W. H., 1957)

β -tetralol. The difference in the effects of tetralin on the eye of the rat and the rabbit may be due to metabolic differences between the species, since alpha tetralol was found to be non-cataractogenic for the rat. Rabbits probably convert tetralin to *ac*- β -tetralylglucuronide which forms *ac*- β -tetralol on hydrolysis (Williams, R. T., 1947).

The toxicity of tetralin vapors was studied by Cardani (1957) in guinea pigs. Three animals were exposed 8 hours a day to a vapor concentration of approximately 275 p.p.m. One guinea pig died after 17 days of exposure and the other two died after 22 days. The principal positive pathological findings in the animals were severe changes in the kidneys and liver and chemical pneumonitis. No significant deviation from normal was found in the peripheral blood.

(B) Human experience

Galewsky (1922) reported an eczematous dermatitis in

painters who had prolonged repeated contact with solvent vapors containing high concentrations of tetralin. According to Koelsch (1926), a group of individuals working with a tetralin-based varnish complained of headache, malaise, vomiting, eye irritation, coughing and rhinitis due to irritation of the mucous membranes of the throat and nose. These men reported that their urine was colored green after exposure to vapors of this varnish. The signs and symptoms of intoxication rapidly disappeared when exposure to tetralin was discontinued (Lehmann, K. B. and Flury, F., 1943). A marked restlessness and central nervous system stimulation was noted in children sleeping in rooms freshly waxed with tetralin-based wax (Rockemann, W., 1922). Several individuals who ingested 5 to 7 g of tetralin per day for an undisclosed number of days also reported a green discoloration of the urine. No additional information is given regarding signs and symptoms of intoxication in these cases (Pohl, J. and Rawicz, M., 1919).

tochemistry

Tetralin vapors or mists containing the hydrocarbon are absorbed into the blood by inhalation. Liquid tetralin is absorbed into the blood from the gastrointestinal tract and probably at a much slower rate through the intact skin. There is no published information on the distribution of tetralin in body tissue, the concentrations attained in the blood or the rate of elimination of the hydrocarbon from the blood and tissues after various routes of administration. Only a small proportion of the tetralin absorbed into the blood is believed to be eliminated unchanged through the lungs (Lehmann, K. B. and Flury, F., 1943).

Pohl and Rawicz (1919) found tetralylglucuronic acid, a dihydro-naphthalene of unknown constitution, and naphthalene in the urine of rabbits, dogs, and humans dosed orally with tetralin. According to Williams (1947), there is some doubt whether some of the reported products of tetralin metabolism are artefacts

of the isolation procedures or naturally-formed substance. There is no doubt, however, that the saturated ring in tetralin is oxidized *in vivo* rather than the aromatic nucleus, which remains unchanged. The subcutaneous injection of tetralin in

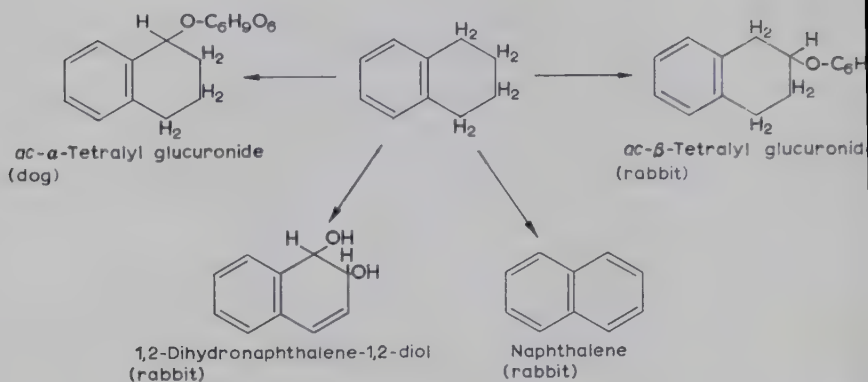


Fig. 77. Urinary metabolites in biotransformation products of tetralin in animals. (Williams, R. T., 1968)

caused a decrease in the urinary sulfate ratio, which indicates that hydroxylation of the hydrocarbon has occurred (see Table 22, p. 76).

The known biotransformation products of tetralin are shown in Fig. 77.

Threshold limit

The threshold limit for tetralin vapor for an 8-hour work shift has not been established. Based on the toxicity studies reported in the literature, a level of 25 p.p.m. appears to be a reasonable figure. This is the threshold limit which has been suggested for naphthalene (see p. 230).

Prevention, detection and treatment of exposure

(A) Prevention

Persons using a tetralin-based varnish, wax or solvent should work under conditions of good general ventilation to minimize

halation of vapors of the hydrocarbon. Care should also be taken to avoid unnecessary contact with liquid tetralin. The use of tetralin in large quantities in industrial plants requires engineering controls and the use of industrial hygiene methods to maintain the atmospheric concentration of the hydrocarbon vapors at a level which is safe for repeated daily exposure. The threshold limit has not been established. A level of 25 p.p.m. appears to be a reasonable value based on the toxicological studies described, the human experience reported with tetralin and the established threshold limits set for chemically related compounds (naphthalene, diphenyl and Dowtherm A). Workers who may be exposed to excessive concentrations of tetralin due to unavoidable circumstances should be provided with suitable protective respiratory equipment. Protective garments and gloves should also be worn if excessive direct contact with the liquid is expected to occur.

B) Detection

A sensitive test has not been established to indicate that exposure to tetralin vapors has occurred or that the absorption of the hydrocarbon has caused biochemical abnormality or latent intoxication. The green-colored urine reported in workers exposed to tetralin-based varnish is evidence of gross over-exposure to the hydrocarbon. The colored compound is in all probability similar chemically to one or more of the metabolites shown in Fig. 77. An analytical method for the determination of these metabolites in microgram quantities in urine could form the basis for an exposure test for tetralin. The validity of the test could be established by correlating the amounts of the metabolites found in the urine with atmospheric concentrations and duration of the exposures under actual working conditions. Since tetralin diminishes the urinary sulfate ratio in animals (see Table 22, p. 76) this may also form the basis for a test for exposure to tetralin. The urinary sulfate test is discussed in detail in Chapter 7 (p. 105).

A periodic health examination should be conducted at regular intervals on workers who may be exposed to tetralin. Each medical examination should include a brief interval medical history, physical examination and complete blood count. The physician should direct his attention to symptoms and signs of eye, mucous membrane, and skin irritation. Systemic intoxication in the absence of this premonitory evidence of exposure to tetralin is highly improbable.

(C) Treatment

The first aid treatment and medical management of acute intoxication due to inhalation of aromatic hydrocarbon vapors is described in Chapter 6, p. 91. Because of its low vapor pressure (1 mm of mercury at 38°) the hazards of acute intoxication due to inhalation of high concentrations of tetralin vapor under normal conditions of use are not great.

The signs and symptoms of chronic tetralin over-exposure such as eye irritation, rhinitis, cough and malaise disappear in a few days after exposure to tetralin is discontinued.

For general discussion of treatment of aromatic hydrocarbon intoxication see Chapter 6, p. 91.

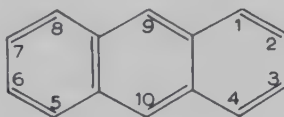
ANTHRACENE

Synonyms

p-Naphthalene; green oil.

Molecular formula: $C_{14}H_{10}$.

Structural formula:



Molecular weight: 178.22.

Physical properties

A crystalline substance with a blueish violet fluorescence (see further table on pp. 202 and 203).

sources, uses and probable modes of contact

Anthracene is obtained by distillation of coal tar, occurring in the portion of the distillate which passes over at a temperature above 500° F. The 'anthracene oil' (also called 'green oil') contains about 2.5-3.5% of anthracene in conjunction with naphthalene, diphenyl, pyrene, and other polycyclic hydrocarbons. The 'green oil' is allowed to stand until the greater part of the anthracene has crystallized out. The solidified portion is then freed from the mother liquor by pressure or by a centrifugal separator is ground up, washed and pressed into 'anthracene cakes' to remove as much as practicable of the paraffin and other impurities.

Purified anthracene is obtained by fractional distillation and repeated crystallization from benzene. Refined anthracene is available commercially in 90-95% purity in the form of white crystalline flakes having a violet fluorescence.

Crude anthracene oil is sometimes employed as a wood preservative and as an agglomerating agent for briquettes. The tawny-brown liquid called *carbolineum*, which is used as a timber preservative, is made by subjecting crude anthracene or green oil to heavy pressure and adding zinc and chlorine. It distills between 570°-735° F following the creosote oils. It was first used by Rhine Valley grape growers in 1876 to preserve posts and poles in vineyards. It is used today by farmers to 'paint' pig-pens, chicken-coops, and barns for the purpose of destroying lice and vermin. It has also been applied directly to the skin of animals for this purpose. Anthracene oil has also been added to sulfonated machine oils because of its lubricating properties, forming an ingredient of the 'Soluble-oil' or 'Screwing mixture'. Anthracene is an important starting material for the synthesis of anthraquinone and alizarin dyes. It is also used to manufacture fluorescent inks, plastics, and novelties such as Christmas tree ornaments. As an absorber of ultraviolet light, anthracene has been used in cellulose ester coatings to prolong film life and in gasoline to inhibit gum formation, to prevent clouding

and impart light stability. Other direct applications for anthracene are as the smoke-making ingredient in pyrotechnic signals and as a constant temperature bath in the manufacture of graphite. When exposed to certain types of radiation, anthracene emits flashes of light which is the basis for its use in scintillation counters.

The most likely mode of contact with anthracene in its industrial use is skin contact with the solid hydrocarbon or with liquid anthracene in crude 'anthracene oil' preparations. Inhalation of anthracene dust or powder and mists or aerosols presents a possible source of direct contact with mucous membranes of the respiratory tract.

Analytical methods

The general physical and chemical methods of analysis for the aromatic hydrocarbons described in Chapter 3 may be adapted for the determination of anthracene. Anthracene forms molecular addition products with nitro compounds and picric acid. The picric acid complex melts at 139° ; the sodium trinitrobenzene complex melts at 164° and the trinitrotoluene complex melts at 162° .

Toxicology

(A) Acute toxicity

Direct contact of anthracene with skin and mucous membranes may cause local irritation depending on the duration of contact. Anthracene is a cutaneous photosensitizer which increases the sensitivity of the skin to solar radiation. It is highly improbable that systemic intoxication could result from the percutaneous absorption of anthracene through the intact skin. Crude anthracene oil has been applied directly to the skin of farm animals for destroying lice and vermin.

Anthracene has a relatively low order of toxicity by the oral route of administration. Only a small fraction of the hydrocarbon administered orally is absorbed from the gastrointestinal

act. Chang (1943) recovered approximately 140 mg of anthracene in the feces of a rat dosed orally with 200 mg of anthracene mixed in a starch solution. Eighty-three % of the anthracene fed in the diet at a level of 1 % was recovered from the feces (see Table 20, p. 71).

3) *Chronic toxicity*

There is considerable information recording human experience with crude commercial preparations of anthracene used in industry. Acute erythema of the skin following exposure to the sun has been reported in 'anthracene workers'. Prolonged contact with crude anthracene preparations causes a bronzing or pigmentation of the skin, especially of the face, forearms and neck (Hueper, W. C., 1942). The hands have a deep brown and occasionally a green color. Small, pink telangiectases and minute actinic keratoses are also found on the face and ulnar aspects of the forearms.

The first cases of occupational anthracene epithelioma of the hands were reported in 1917 by Lehmann, who noted the occurrence of warts, eczemas and hyperkeratoses of the hands, arms, forearms, knees and chest in 22 out of 30 workers employed in an anthracene plant. Three of these workers had also developed basal cell cancer. Histologically, the lesions are cornified squamous epitheliomas which grow slowly and do not readily metastasize. The occurrence of epithelioma in workers exposed to crude anthracene oils was suspected in 1913. 'Anthracene epithelioma' was reported in workers in a grease factory, and in men employed in an anthracene and alizarin plant. Workers handling the crude 'anthracene cake' were most affected, men dealing with the purified product being but slightly affected (Hueper, W. C., 1942).

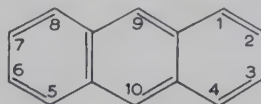
Because of the chemical complexity of the crude anthracene preparations to which workers were exposed, the actual carcinogen in these mixtures is unknown. Kennaway (1924) produced cancer in mice by repeated skin application of 'green oil'

and anthracene oil but found no tumors in mice after repeated cutaneous painting with anthracene itself dissolved in benzene. It was concluded that the cancer producing substances were not present in the solid fraction of the anthracene oil. Anthracene and a number of aliphatic and cyclic derivatives of anthracene have not produced skin cancer in mice after repeated topical skin application (Table 43).

TABLE 43

ANTHRACENE AND DERIVATIVES WHICH HAVE NOT PRODUCED SKIN TUMORS IN MICE BY REPEATED TOPICAL APPLICATION*

I. *Anthracene*:



II. *Anthracene derivatives*:

Mono-alkyl or non-condensed aryl

Methyl 2, 9; ethyl 9; phenyl 1, 2, 9.

Di-alkyl or non-condensed aryl

Isopropyl 1,5; methyl 1,2; 1,3; 1,4; 2,3; phenyl, benzyl, or α -naphthyl 9, 10, phenyl 9, naphthyl 10.

Polyalkyl and hydrogenated
Methyl 2, 3, 6, 7.

Octahydro.

Condensed aryl
1:2,3:4,5:6-Tribenz-
1',2' and 2',1' anthra-1,2-
1,2 (1',2'-naphth)-
2',3'-naphth- and 2',3'-
phenanthra-1,2-
7:7',9:10-dimethyl 2',3'-
naphtho-1,2-

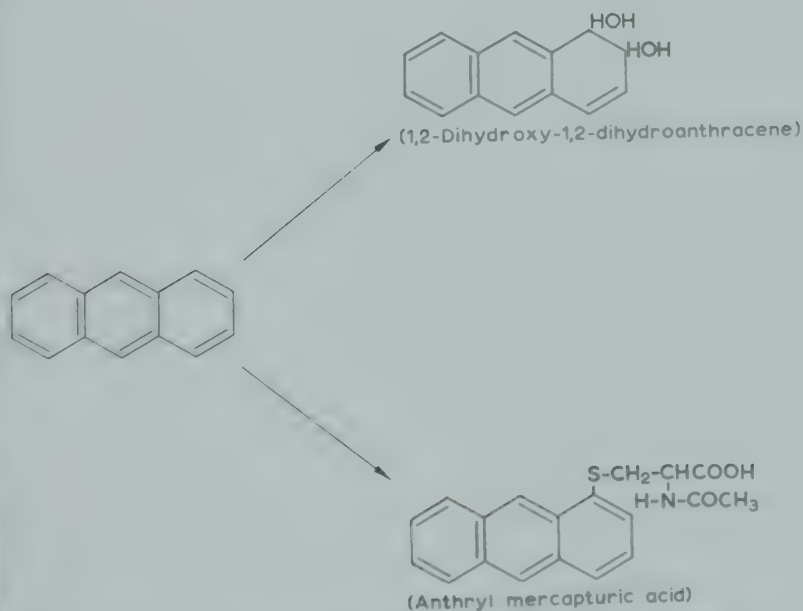
* Compiled from Hartwell, J. L. (1951) and Shubik, P. and Hartwell, (1957).

A lesion of the skin of the eyelid (not the conjunctival membrane) believed to be due to contact with anthracene fuel has been reported in workers handling crude anthracene (Occupation and Health, Vol. I, 1930). The repeated administration of anthracene to experimental animals by various routes of administration indicates that the hydrocarbon has a relative

order of chronic toxicity. Schmahl and Reuter (Shubik, P. Hartwell, J. L., 1957) fed 31 rats 6 mg of anthracene daily for 33 months. At the end of one year of daily dosing 22 rats were alive and none had developed tumors at the termination of the experiment. Anthracene was injected intraperitoneally in mice for 7 days at a dose of 500 mg per kg of body weight. Out of 10 animals dosed 9 survived and showed some depression of weight gain as compared with the control animals (see Table 47). Four out of 5 rats survived at the end of 4 months of weekly subcutaneous injections of 5 mg of anthracene dissolved in sesame oil (Hartwell, J. L., 1951).

Chemistry

Anthracene is poorly absorbed from the gastrointestinal tract as shown by Chang's work with rats dosed orally with the hydrocarbon (Table 20, p. 71). Although there is no experimental evidence to support the statement, it is probable that anthracene



- 78 *Metabolic transformation of anthracene in the rabbit.*
 (Boyland, E. and Levi, A. A., 1935, 1936).

is poorly absorbed through the intact skin so that systemic intoxication by percutaneous absorption is highly unlikely. After absorption into the blood, anthracene is converted, presumably in the liver, into hydroxyl derivatives which are excreted in urine as water-soluble metabolites. The biotransformation of anthracene in experimental animals are shown in Fig. 78.

Threshold limit

The threshold limit for anthracene for an 8-hour workday has not been established.

Prevention, detection and treatment of exposure

(A) Prevention

The chemist, technician and worker using relatively small quantities of anthracene should be careful in handling and transferring the solid in order to minimize skin contact as well as inhalation of fine dust of the hydrocarbon. In industrial plants using large quantities of anthracene it is important to employ engineering controls and industrial hygiene methods to maintain the concentration of the hydrocarbon dust at a level which is safe for repeated daily exposures. There is insufficient toxicological information available to form a sound basis for suggesting a tentative value for the maximum allowable concentration of anthracene. It is important to emphasize that anthracene and a number of alkyl derivatives are not considered to be carcinogenic hydrocarbons (see Table 43). The skin cancers reported in 'anthracene' workers are believed to have originated from contact with polynuclear aromatic hydrocarbons present as contaminants in the crude 'Green oil'. See Chapter 12 for further discussion of carcinogenic polycyclic aromatic hydrocarbons. A Threshold Limit of approximately 0.1 mg/m³ of air is suggested for anthracene. This is based on the toxicological information available and analogy with hydrocarbons for which threshold limits have been established.

3) Detection

There is no established biochemical test to ascertain if exposure to anthracene has occurred or if sufficient anthracene has been absorbed under actual working conditions to cause sub-clinical or incipient systemic toxicity. An exposure test based on the concentration or total 24-hour urinary output of anthracene or a metabolite may form the basis for such a test. Newer analytical techniques for the quantitative analysis of the polycyclic aromatic hydrocarbons have remarkable sensitivity (see Chapter 12, p. 253). These methods may make it possible to determine the sub-microgram quantities of anthracene that might be present in the urine of workers exposed to the hydrocarbon.

A periodic health examination should be conducted annually in individuals who are actually exposed to anthracene in their work. The examination should include a brief interval medical history and physical examination. Although there is no reason to suspect any effect on the hemopoietic tissue, caution indicates that a complete blood count should be included for the record. The physician should focus his attention on symptoms of eye, skin and respiratory tract irritation, keeping in mind the fact that direct exposure to sunlight aggravates dermatitis due to anthracene.

4) Treatment

Acute intoxication by inhalation of anthracene fumes or vapor can not occur except under unusual conditions such as exposure to the hydrocarbon at an elevated temperature in a confined space. The first aid treatment and medical management of acute intoxication due to inhalation of volatile aromatic hydrocarbons is described in Chapter 6, p. 91.

The treatment of accidental ingestion of anthracene consists in emptying the stomach by the induction of vomiting and/or gastric lavage followed by the administration of demulcents such as milk or egg white. Subsequent treatment is symptomatic and supportive.

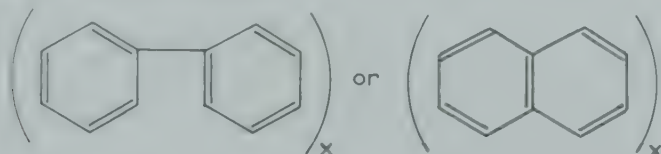
Chronic anthracene intoxication presents the clinical picture of irritation of the eyes and mucous membranes of the respiratory tract and skin irritation which is made worse by exposure to direct sunlight. The individual responds favorably following removal from the source of exposure to anthracene.

Polycyclic aromatic hydrocarbons

Synonyms

polyaromatic hydrocarbons, polynuclear hydrocarbons.

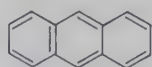
General structural formula:



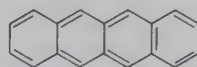
Physical properties

The polycyclic aromatic hydrocarbons, which are essentially colorless, are solids at room temperature. Most of the polycyclic aromatic hydrocarbons are colorless although some are colorful as shown in Fig. 79. They have a low vapor pressure at room temperature, boil above 200° and have high melting points. They are insoluble in water and in the usual organic solvents. Slightly more soluble in the lower aromatic hydrocarbons. An interesting property of the polycyclic aromatic hydrocarbons is their solubility in purines. The solubility decreases with the number of condensed rings. With an equal number of rings, the angular configuration is more soluble than the linear arrangement (Weil-Malherbe, H., 1946). The solubility of the polycyclic aromatic hydrocarbons in aqueous caffeine is used in the analytical-chemical test for the carcinogenic potency of high boiling petroleum hydrocarbons (see Chapter 3, p. 37). The polycyclic aromatic hydrocarbons absorb in the ultraviolet and

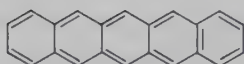
infrared portion of the electromagnetic spectrum and may exhibit the property of fluorescence. Some polycyclic aromatic hydrocarbons such as anthracene and diphenylhexadiene possess



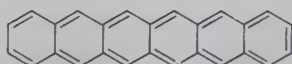
Anthracene
(colorless)



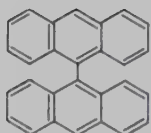
Naphthalene II
(orange)



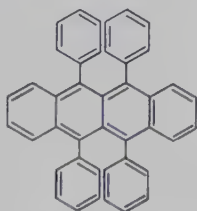
Pentacene
(blue)



Hexacene
(green)



9,9'-Dianthryl
(yellow)



Rubrene
(red)

Fig. 79. The relationship between color and constitution of linear polycyclic aromatic hydrocarbons.

the property of scintillation. Many polycyclic aromatic hydrocarbons form complexes (picrates, styphnates) which are useful for isolation, purification, and quantitative analysis.

Sources, uses and probable modes of contact

The polycyclic aromatic hydrocarbons are derived commercially from coal and petroleum and occur in smaller quantities in fossilized pine wood, peat and lignite. They are also formed by pyrolysis of combustible organic matter such as tobacco, coffee, and motor fuels. The wide variety of polycyclic aromatic hydrocarbons formed by combustion of tobacco, coffee and

tor fuels is shown in Tables 44, 45 and 46. These compounds of interest because of the possible health hazard associated with their presence in community air.

TABLE 44
POLYCYCLIC AROMATIC HYDROCARBON
COMPOSITION OF CIGARETTE-SMOKE CONDENSATE*

<i>Hydrocarbon</i>	<i>µg/100 cigarettes</i>
Alkylchrysene	0.04
Benzo[a]pyrene	0.50
Benzo[e]pyrene	0.30
Benzo[mno]fluoranthene	0.10
3:4-Benzopyrene	0.70
Chrysene	0.06
Dibenz[a,h]anthracene	0.05
Fluoranthene	5.0
4-Methylpyrene	5.0
Pyrene	5.0

after Van Duuren, B. L., 1958.

TABLE 45
POLYCYCLIC AROMATIC HYDROCARBON
COMPOSITION OF COFFEE SOOT*

<i>Hydrocarbon</i>	<i>µg/kg</i>
Benz[a]anthracene	16
Benzo[k]fluoranthene	70
Benzo[a]pyrene	200
Benzo[e]pyrene	190
Benzo[ghi]perylene	100
Chrysene	530
Fluoranthene	340
Perylene	280
Phenanthrene	130
Pyrene	260

after Kuratsune, M. and Hueper, W. C., 1958.

TABLE 46
POLYCYCLIC AROMATIC HYDROCARBON
COMPOSITION OF VEHICULAR EXHAUST SOOT*

<i>Hydrocarbon</i>	<i>Gasoline exhaust</i>	<i>Diesel exhaust</i>
3:4-Benzpyrene (p.p.m. free carbon)	1570	20
Pyrene (p.p.m. carbon)	440	820
Anthracene (p.p.m. carbon)	385	60
1:2-Benzanthracene (p.p.m. carbon)	180	—
3:4-Benzofluoranthene**	+	+
Naphthacene	+	—
Pentaphene	+	+
1:2,3:4-Dibenzopyrene	+	+
11:12-Benzofluoranthene	+	+
1:2,9:10-Dibenzotetracene	+	+
1:2,4:5-Dibenzopyrene	+	—
1:12,2:3-Dibenzoperylene	+	—

* After Lyons, M. J., and Johnston, H. (1957) and Lyons, M. J. (1957)

** (+) identified (—) not identified.

The polycyclic aromatic hydrocarbons are natural components of lubricants, fuels (see Chapter 13) and construction materials (coal, petroleum, pitch and tar). Some polycyclic aromatic hydrocarbons have found specific applications as starting materials for synthesis in the chemical industry (anthracene, Chapter 11), as constituents of heat-exchange mixtures (*p*-terphenyl) and as scintillators (stilbene, 1,1,4,4-tetraphenylbutadiene-1,3,5). Polyphenyl hydrocarbons show an unusually high resistance to pyrolysis (decomposition by heat) and radiolysis (decomposition by radiation) compared with aliphatic hydrocarbons (Colichman, E. L. and Fish, R. F., 1957).

The most widespread mode of contact with the polycyclic aromatic hydrocarbons is by inhalation of hydrocarbon particulates formed in smoking tobacco and by exposure to community air contaminated with combustion products (vehicular exhaust).

and industrial effluents). Skin contact and inhalation of mists may occur in individuals working with individual aromatic hydrocarbons or with mixtures containing them.

Analytical methods

The polycyclic aromatic hydrocarbons in the atmosphere can be determined by air sampling with suitable collection equipment (membrane filters), dissolving or eluting the particulates with a solvent, and subsequent analysis by the general methods described in Chapter 3. The current interest in air pollution has resulted in a rapid development of sensitive analytical methods for the polynuclear hydrocarbons. Among the colorimetric methods are identification of the hydrocarbon by means of oxidation, or treatment with piperonal, 3-nitro-4-dimethylamino-benzaldehyde or isatin. Fluorescence spectrometry offers both a qualitative and quantitative method of analysis. The sensitivity of some of the tests is in the range of $\text{m}\mu\text{g}$ per ml or parts per million.

Toxicology

1) General

There is very little published information relevant to the toxicity of the polycyclic aromatic hydrocarbons in experimental animals other than the mouse. By the oral route of administration, the acute toxicity is expected to be relatively low because the complex hydrocarbon molecules are poorly absorbed from the gastrointestinal tract (see Table 13, p. 55). In skin painting experiments conducted with mice for the study of carcinogenesis, a concentration of polynuclear hydrocarbons is usually so low (ca. 1%) that toxic effects are not produced in a single dose. The repeated topical application of polycyclic aromatic hydrocarbons dissolved in a solvent (acetone, benzene) causes systemic effects indicating that the polynuclear hydrocarbons are absorbed percutaneously. Shubik and Della Porta (1957) have described acute studies in mice treated with large doses of certain

polycyclic aromatic hydrocarbons. Dimethylbenzanthracene (DMBA) showed an acute lethal effect when applied topically to the skin and when injected intraperitoneally in mice. Benzo[a]pyrene (BP) and methylcholanthrene (MC) showed a similar effect only after intraperitoneal injection of a single large dose. Anthracene and fluorene administered under the same conditions failed to produce any toxic effects. In the skin painting experiments

TABLE 47
TOXICITY OF POLYCYCLIC AROMATIC HYDROCARBONS IN MICE
(500 mg/kg/day, intraperitoneal, 7 days)*

<i>Hydrocarbon</i>	<i>No. of animals</i>	<i>No. of deaths</i>	<i>Weight change treated/control</i>
Acenaphthene	5	1	0.0/—0.5
Acenaphthylene	10	1	—0.5/+0.5
Anthracene	10	1	0.0/+10
9,9'-Bianthryl	10	1	0.0/+0.5
<i>p</i> -Di- <i>p</i> -tolylbenzene	5	2	+0.5/—0.5
1,4-Dimethyl-3,5,6-triphenylbicyclo-[2,2,1]heptene-5	10	1	+1.5/+1.5
Fluoranthene	10	0	70.5/+0.5
Methylstilbene	9	0	+0.9/+2.1
Methylene-2,3,3,4,5,-pentaphenyl-Δ, 3-cyclopentene	10	0	0.0/+0.5
1,2,3,4,5,6,7,8-Octahydrophenanthrene	10	0	—1.6/—0.9
1,2,3,4,5-Pentaphenyl-7-benzo-[2,2,1] bicycloheptene-2	10	2	+1.0/0.0
1,2,3,4,5-Pentaphenylcyclopentadiene	10	1	0.0/+2.5
Pyrene	5	1	—1.0/—0.5
<i>o</i> -Terphenyl	10	1	0.0/+1.5
Tetraphenylbenzene	10	1	+1.0/+1.5
1,1,3-Trimethyl-3-phenylindane	5	1	—0.5/+0.5

* Compiled from Cancer Research Supp. 2 (1955); (1948).

nts, the dosage varied with the solubility of the various hydrocarbons, being 1.5% for BP and 2% for MC and DMBA in acetone. Each dose consisted of approximately 0.08 ml of solution. Groups of 12 mice received repeated applications 6 days a week for varying periods up to 19 weeks.

An additional experiment was conducted in which DMBA (10 mg. per kg of body weight) was applied to a large shaved area of skin in a 2% solution in acetone. Two animals died and were moribund on the 7th day after dosing; five other mice died or were moribund by the 11th day.

The pathological picture induced by the 3 carcinogenic hydrocarbons (BP, MC and DMBA) was essentially morphologically similar although with quantitative variations. Myelo-, erythro-, and lymphopoiesis were markedly affected, with involvement of the peripheral blood, spleen, lymph nodes and bone marrow. The absence of pathological change in other organs, with the exception of the testes and intestinal mucosa, was striking.

The toxicity of a number of polycyclic aromatic hydrocarbons to mice by the intraperitoneal route of administration is shown in Tables 47 and 48.

1) Carcinogenesis

The induction of cancer by chemicals is such an extraordinary biological response that it requires special treatment. Some of the polycyclic aromatic hydrocarbons are unique among hydrocarbons in possessing this property for inducing new or abnormal growth in tissue.

The first pure chemical to manifest pronounced carcinogenic properties when tested in animals was 1:2,5:6-dibenzanthracene (Addow, A., 1958). He identified 3:4-benzpyrene as the active substance in carcinogenic pitch.

The word 'carcinogen' requires explanation since its meaning is far beyond the etymology of the word: 'capable of causing cancer'. Strictly speaking, glucose, fructose and sodium chloride are 'carcinogens' because concentrated solutions of these che-

TABLE 48

TOXICIT

<i>Hydrocarbon</i>
Acenaphthylene
Benzene- <i>m</i> -di- <i>a</i> -naphthyl
1,3-Butadiene- <i>trans</i> , <i>trans</i> -1,4-diphenyl
3-Methyl cholanthrene
1-(2-Biphenyl)-3-(4-biphenyl)-1,3-cyclohexadiene
1,3-Bis(2-biphenyl)-1,3-cyclohexadiene
9,10-Diphenylanthracene
1,3-Diphenyl-2-butene
1,1-Diphenyl-2,2-dimethylpropane
1,1,1-Triphenylethane
Diphenyl- <i>p</i> -tolylmethane
9-Methylanthracene
<i>p</i> -Methyldiphenyl
1,2,3,4,5,6,7,8-Octahydroanthracene
9-Phenanthryldiphenylmethane
Triphenylethylene

* Compiled from Cancer Research Supp. No. 1, (1953); 18, No. 8 (19

CYCLIC AROMATIC HYDROCARBONS*

(mice-intraperitoneal)

<i>Dose</i> <i>mg/kg</i>	<i>Dose</i> <i>frequency</i>	<i>No.</i>	<i>No. of</i> <i>animals</i>	<i>No.</i> <i>deaths</i>	<i>Weight change</i> <i>treated/control</i>
150	b.i.d.	14	5	0	— 0.5/+ 0.5
300	quotid.	7	5	0	+ 1 /— 2
125	quotid.	7	10	0	— 1.9/— 4.1
250	quotid.	14	20	4	— 0.5/+ 0.5
300	quotid.	7	5	0	0.0/+ 0.5
300	quotid.	7	5	0	
150	b.i.d.	14	5	0	— 5.0/— 1.0
200	b.i.d.	7	5	1	— 2.5/+ 2.0
125	quotid.	7	5	1	— 1.0/— 2.0
300	quotid.	7	5	0	0.0/+ 0.5
300	quotid.	7	5	0	— 1.5/— 2.0
250	b.i.d.	13	10	2	+ 1 /+ 2.1
ca. 50	quotid.	4	10	0	
200	b.i.d.	14	5	0	
150	b.i.d.	14	5	0	
150	b.i.d.	14	5	0	

micals injected subcutaneously into the rat have induced occasional sarcomata (Boyland, E., 1958). These chemicals are regarded as carcinogens by most authorities in spite of this finding. It is believed that the sarcomata were probably caused by the effect of the osmotic pressure of the injected solution rather than by the specific chemical action of these substances. Human experience with these chemicals, one of which is essential to life, minimizes the importance of the observation that connective tissue tumors are formed by the subcutaneous injection in rats.

The significance of the observation that the subcutaneous



Fig. 80. Cutaneous cancer in worker exposed to shale oil.

(Eckardt, R. E., 19

plantation of certain plastics in rats and mice produces comata is still not clear. Eckardt (1959) has pointed out that plastics are to be implanted in human tissues (wrapping of aneurysms, artificial heart valves) post-mortem observation of the tissues in contact with these plastics will help determine the significance of this observation in experimental animals.

The discovery that the repeated topical application of certain chemicals to the skin of mice and rabbits causes tumors is of great practical importance. This is because many industrial chemicals come in contact with the skin of workers. The re-



81. Rabbit ear showing multiple tumors due to repeated topical application of carcinogenic substance. (Eckardt, R. E., 1959).

peated topical application to the skin of experimental animals simulates the manner of contact in industry. Furthermore, knowledge that coal tar, shale oils, coal pitch, certain unre-
 mineral oils and other materials are known to cause skin cancer in man magnifies the significance of the finding that a chemical produces a tumor by repeated application to the skin (Fig. 82). Historically skin cancer was recorded in man long before it was produced in animals by skin painting. Sir Percival Pott described the 'soot-wart' in 1775; it was not until 1914 that Yamagiwa and Ichikawa discovered that if the ears of a rat are painted with coal tar over long periods of time, warts

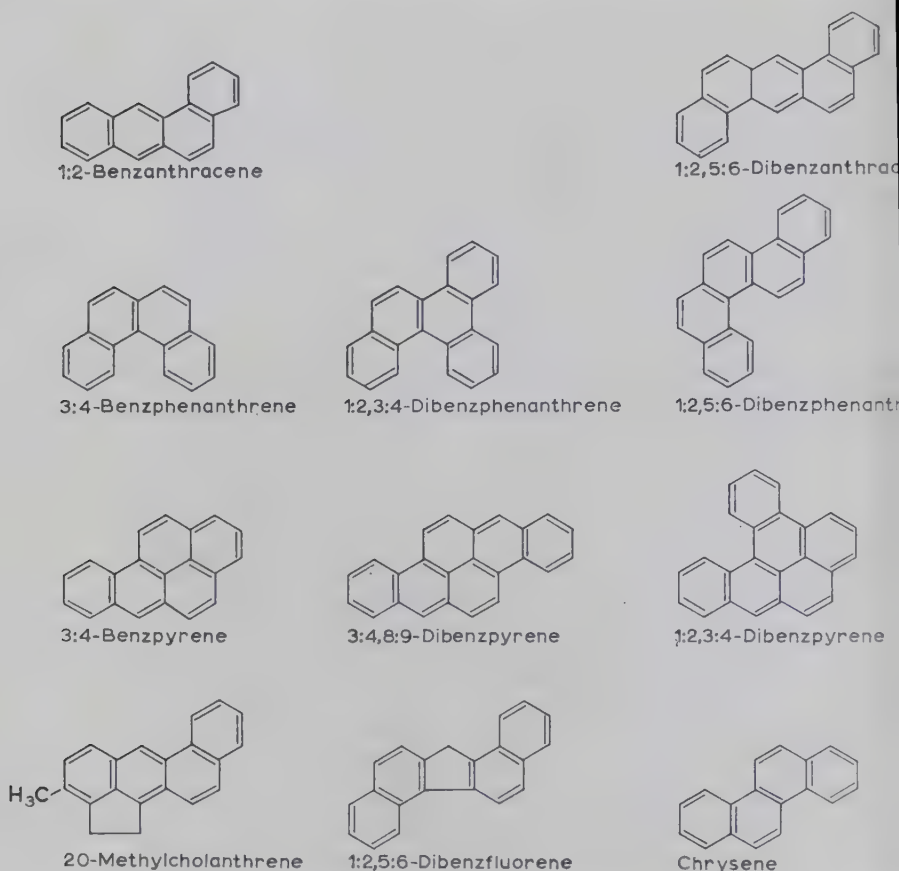


Fig. 82. Principal molecular types of polycyclic aromatic hydrocarbons which have produced tumors in mice by repeated topical application.

TABLE 49

OLYCYCLIC AROMATIC HYDROCARBONS WHICH HAVE PRODUCED
KIN TUMORS IN MICE BY REPEATED TOPICAL APPLICATION*

2. *Benzanthrane and derivatives*
o-Alkyl
ethyl in 2',3,4,4',5,6,7,8,9,10.
n-ethyl, *n*-propyl, *n*-butyl, *n*-
n-ethyl, *n*-hexyl, *n*-heptyl, phenyl
5.
propyl in 5,6.
alkyl
ethyl in (5,6), (6,7), (6,8),
10).
n-ethyl in (9,10).
alkyl
ethyl in (5,9,10), (6,9,10).
ethyl in (9,10), *n*-propyl in 5.
Alkyl and Alicyclic
ethyl in (5,6,9,10).
-and 6,7-Cyclopenteno,
methyl-5,6-cyclopenteno.
2,5:6-Dibenzanthracene and
atives
o-Alkyl
ethyl in 2',3',4.
alkyl
ethyl, *n*-butyl, benzyl in
10).
0-Dihydro.
1,3:4-Dibenzanthracene
0-Dimethyl-1:2,7:8-Diben-
racene
5. *Phenanthrene derivatives*
1-Methyl, 3-isopropyl.
1,2,4-Tri- and 1,2,3,4-tetra-
methyl.
1,2-Cyclopenteno; 10-methyl-
cyclopenteno.
3',3',9-Trimethylcyclopenteno.
6. *3:4-Benzphenanthrene and
derivatives*
Methyl in 1,2,6,7 or 8.
Ethyl, *n*-propyl or isopropyl
in 2.
7. *1:2,3:4-and 1:2,5:6-Dibenz-
phenanthrene*
8. *3:4-Benzpyrene and derivative*
Isopropenyl in 10.
9. *1:2,3:4-Dibenzpyrene and
derivatives*
Methyl in 7; phenyl in 5.
10. *3:4,8:9-Dibenzpyrene*
11. *Chrysene and derivatives*
5,6-Dimethyl, 5,6-diphenyl.
12. *Cholanthrene and derivative*
20-Methyl.
13. *Miscellaneous*
1:2,3:4-, 1:2,5:6- and 1:2,7:8-
Dibenzfluorene.
Pyrene, tetraphenylmethane.
Acenaphthanthracene, phenan-
thra-acenaphthene.
9,10-Dimethylantracene;
α-ethyl-*β*-*sec*-butylstilbene.

Compiled from Hartwell, J. L. (1953); Shubik, P. and Hartwell, J. L.
1959.

TABLE 50

MONO-, DI-, AND TRICYCLIC AROMATIC HYDROCARBONS
WHICH HAVE NOT PRODUCED SKIN TUMORS IN MICE
BY REPEATED TOPICAL APPLICATION*

I. *Monocyclic*

Benzene

Toluene

Styrene

Xylenes

II. *Dicyclic*

Diphenyl (biphenyl)

Diphenylhexane, diphenylhexadiene

 α - α -Diphenyl- β -ethyl- α -butylene or amylene α - α -Diphenyl- β -methyl- α -propylene

Naphthalene and derivatives:

Dihydro; tetrahydro; 1,2-diethyl

III. *Tricyclic*

1,4-Distyrylbenzene

 α - α - β -Triphenyl- α -butylene

Triphenylethylene

 α -Phenylnaphthalene

Acenaphthene, acenaphthylene

Anthracene and derivatives:

9 Methyl or ethyl, 2-methyl, octahydro

Dimethyl (1,2), (1,3), (1,4) or (2,3)

Di-isopropyl (1,5), 2,3,6,7-tetramethyl

Phenanthrene and derivatives:

1,9-Dimethyl, octahydro

Fluorene

* Compiled from Hartwell, J. L. (1953) and Shubik, P. and Hartwell, J. (1957).

papillomas and cutaneous horns develop and eventually epidermal tumors may be produced (Fig. 81). This observation opens up a new field of biological research—experimental carcinogenesis.

is. Although this is a relatively new field in which an enormous amount of work has been conducted, there is today no standard carcinogenic test' (Eckardt, R. E., 1959). Much more experimental and thought are needed to improve and develop methods for testing for carcinogenic activity, and they cannot be rigidly specified at the present time (Boyland, E., 1958). Thorough discussions of the interpretation and limitations of experimental carcinogenesis are presented by Eckardt (1959) and Boyland (1958).

It is generally agreed that the route of administration of a substance to be tested should depend on the proposed use of the product. Skin painting is particularly suitable for testing products which might be applied to the skin in actual use. The principal molecular types of polycyclic aromatic hydrocarbons and the specific compounds which have produced skin tumors in mice by repeated topical application are shown in Fig. 82 and Table 49 respectively. Tables 50, 51 and 43 (pp. 262, 264 and 265) list the aromatic hydrocarbons which have been tested by repeated topical application and have not produced tumors in mice. The amounts of different polycyclic aromatic hydrocarbons necessary to induce cancer in 50% of the treated animals (ED_{50}) varies greatly. A polycyclic hydrocarbon is regarded as a weak carcinogen: (1) if it produces cancer in small proportions of animals, even with optimal doses, (2) if large doses are required, (3) if it is slow in acting. The ED_{50} values for 1:2,5:6-dibenzanthracene, 20-methylcholanthrene, and 3:4-benzpyrene are 20 and 80 μg respectively for the mouse. See Fig. 83, p. 266. The only quantitative studies reported to date on the carcinogenicity of the polynuclear hydrocarbons by inhalation are those described by Kuschner *et al.* (1957). No lung tumors were found in rats after one hour exposures, 5 times weekly for 6 weeks, to atmospheric concentrations of 41.1 mg of methylcholanthrene per cubic meter of air. The methylcholanthrene was used in a variety of forms including a pure fume, a saline dispersion, an oil solution and a solid paraffin aerosol of the

TABLE 51

POLYCYCLIC AROMATIC HYDROCARBONS WHICH HAVE NOT
PRODUCED SKIN TUMORS IN MICE BY REPEATED TOPICAL
APPLICATION*

- I. *Cyclic derivatives of naphthalene*
1,1'- and 2,2'-Dinaphthyl
Di-2-naphthylethylene
1-Isopropenylnaphthalene (dimer)
- II. *Cyclic derivatives of anthracene*
mono-Phenyl-1, 2 or 9;
9,10-Diphenyl, dibenzyl or di- α -naphthyl;
9-Phenyl, 10- α -naphthyl.
1:2-(1':2'-Naphth); 2':3'-naphth-1:2-;
9,9'-Dianthryl; 2':3'-phenanthra-1:2-;
1':2'-Anthra-1:2- and 2':1'-anthra 1:2-;
7,7'-Dimethyl-2'3'-naphtho-1:2-;
10,10'-Diphenyl-9,9'-dianthryl.
1:2,1':2'-Dibenz-6,6' (or 7,7')-dianthryl.
Benzanthrene; 10-benzylacenaphthanthracene.
Anthanthrene; 1:2,3:4,5:6-tribenzanthracene.
- III. *1:2-Benzanthracene and derivatives*
Methyl in 2' or 3'; isopropyl in 3, 7 or 10.
Dimethyl (2',6), (2',7), (3',6) or (3',7).
5-Ethyl-7,8-dihydro-; 5-ethyl-9,10-dimethyl.
6-Phenyl; 10-benzyl; 9,10-diphenyl.
9,10-Dimethyl-1:2,3:4-dibenzanthracene; 1:2,3:4-dibenzanthracene.
cis-9,10-Dimethyl-9,10-dihydro-1:2,5:6-dibenzanthracene.
- IV. *Cyclic derivatives of phenanthrene*
1:2- and 3:4-Cyclopenteno.
3,9-Dimethylcyclopenteno; 3' or 9-Methylcyclopenteno.
2':3'-Naphtho-1:2- or 2':3-.
3',3',9-Trimethylcyclopenteno; 2':3'-phenanthra-2:3-.
3:4,5:6-Dibenzphenanthrene.
- V. *Naphthacene and derivatives*
9,10-Dihydro; tetrahydro; tetramethyl.
 β -Isopropyl; 9,10,11,12-tetraphenyl.

9,12,10,11-Diphenylene-9,10-diphenyl-9,10-dihydro-;
9,12,10,11-Diphenylene-.

Fluoranthene and derivatives

2,4-Dimethyl; 2,3,4-trimethyl;
2,2,4-Trimethyl-1,2-dihydro-;
2,2,4-Trimethyl-1,2,3,4-tetrahydro-.

Cyclic derivatives of fluorene

3:4-Benzfluorene; chrysofluorene.
3:4,5:6-Dibenzfluorene; 9-methyl-1:2,5:6-dibenzfluorene.
5-Methyl-8-isopropyl-2':1'-naphtho-1:2-;
8-Methyl-2':1'-naphtho-1:2-;
1':2'-Naphtho-2:3-; and 2':3'-naphtho-2:3-.
Phenanthrafluorene.

Chrysene derivatives

2-Isopropyl.
4:5-Benz-10:11-(1':2'-naphtho-).
2:3,8:9-Di-(1':2'-naphtho-).

Pyrene and 3:4-Benzpyrene derivatives

s- and *as*-Hexahdropyrene.
4-Methylpyrene; 2':3'-Naphtho-3:4-pyrene.
3'-Methyl-3:4-benzpyrene;
1',2',3',4'-Tetrahydro-3:4-benzpyrene.

Miscellaneous

s-Triphenylbenzene; triphenylene.
Dodecahydrotriphenylene; 7,8-dihydrophenalyl-1-7-spirocyclo-
pentane; *bis*-diphenylene-ethylene; polyacenaphthylene.
1-Methyl-3:4-benzanthracene; pentacene; picene.
Perylene; dinaphthoperylene; pentaphenylethane.
Truxene; retene; dehydronorcholene.
Cholestene; Δ -2,4-cholestadiene.
1:2-Cyclopenteno-acenaphthene-3'-spirocyclo-2''-methylcyclo-
hexane.

meso-Dihydrocholanthrene.

1,2,3,4,5,6,7,10,17,20,22,23-Dodecahydrocholanthrene.

Compiled from Hartwell, J. L. (1951); Shubik, P. and Hartwell, J. L. (1957).

hydrocarbon. The particle size of the hydrocarbon was mass median diameter. In additional experiments with mice and rats no lung tumors comparable to the common human bronchogenic tumor (squamous or undifferentiated carcinoma of bronchial origin) were observed after 267 repeated exposures extending over an observation period of 772 days.

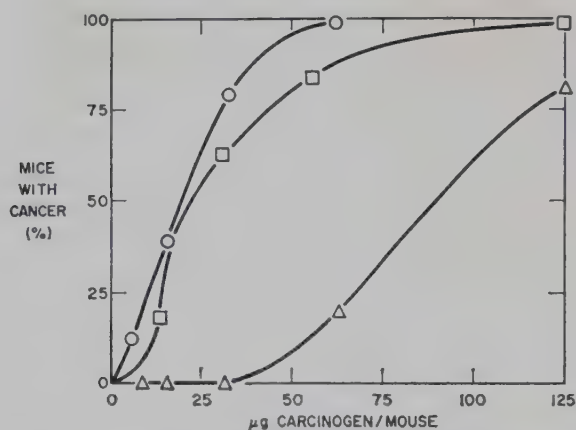


Fig. 83. Dose response relationships for three carcinogenic polycyclic aromatic hydrocarbons. Topical application to skin. \circ = 1:2,5:6-dibenzanthracene; \square = 20-methylcholanthrene; \triangle = 3:4-benzpyrene.

(Boyland, E., 1961)

Biochemistry

The polycyclic aromatic hydrocarbons are poorly absorbed from the gastrointestinal tract when incorporated in the diet or given as a suspension in aqueous media (Table 20, p. 7). Toxicological studies conducted with animals dosed repeatedly by topical application with polycyclic aromatic hydrocarbons in hydrocarbon solvents indicate that percutaneous absorption may occur under these conditions. It is highly improbable that the hydrocarbons when applied as solids could be absorbed through the intact skin at a sufficiently rapid rate to cause systemic intoxication.

A suspension of benzpyrene injected intravenously is stored in the liver, lung, kidney, and adipose tissue and then metabolized

and excreted. In some experiments from 60-80% of the pyrene injected has been accounted for as metabolites (Seibert *et al.*, 1947).

Because of their lipid solubility it is expected that after absorption into the blood stream the polycyclic aromatic hydrocarbons would tend to accumulate in fatty tissues. Since their vapor pressure is low, pulmonary exhalation, which plays an important role in the elimination of volatile hydrocarbons, is negligible with the polynuclear hydrocarbons. Lorenz and Hesse (1936) were able to detect 1:2,5:6-dibenzanthracene in tumors produced several months after a single subcutaneous injection into mice. This indicates that the polycyclic aromatic hydrocarbons are transformed slowly into soluble metabolites or do not readily diffuse in tissues. Both of these factors favor accumulation in the body. The metabolites are excreted principally in the urine but may be found in the feces after the subcutaneous or intraperitoneal injection of the hydrocarbon. The principal metabolic pathway of the polycyclic aromatic hydrocarbons is similar to the *in vivo* mechanism of hydroxylation described for naphthalene and anthracene. The metabolism of naphthalene and anthracene has been discussed in Chapter 11.

Elson *et al.* (1945) found an increased excretion of urinary mercapturic sulfate after administration of phenanthrene to the rat, indicating that hydroxylation of the hydrocarbon had occurred. The studies of Young (1947) and Boyland and Wolf (1950) indicate that phenanthrene undergoes perhydroxylation in the body. Dihydrophenanthrene diols were isolated from the urine of rats and rabbits dosed with phenanthrene. These biotransformations of phenanthrene are shown in Fig. 84.

Two derivatives of fluorene were isolated by Neish (1948) from the urine of rabbits dosed with the hydrocarbon. One of these was identified as 2-hydroxyfluorene, the other had the properties corresponding to the dihydrate of the glucuronide of fluorene (Fig. 84).

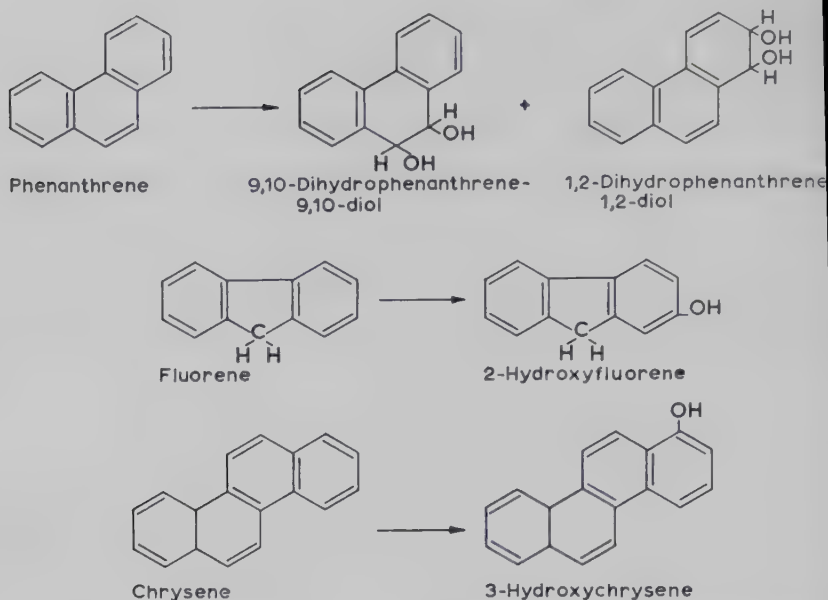


Fig. 84. Biotransformation of phenanthrene, fluorene and chrysene in animals (Young, L., 1968).

Berenblum and Schoental (1949) isolated 3-hydroxychrysene from the feces of rats dosed intraperitoneally with the hydrocarbon (Fig. 84). According to Harper (1957, 1958) pyrene is metabolized in the rat and mouse to a variety of products which are excreted in the urine and the feces. In the feces, 3-hydroxy

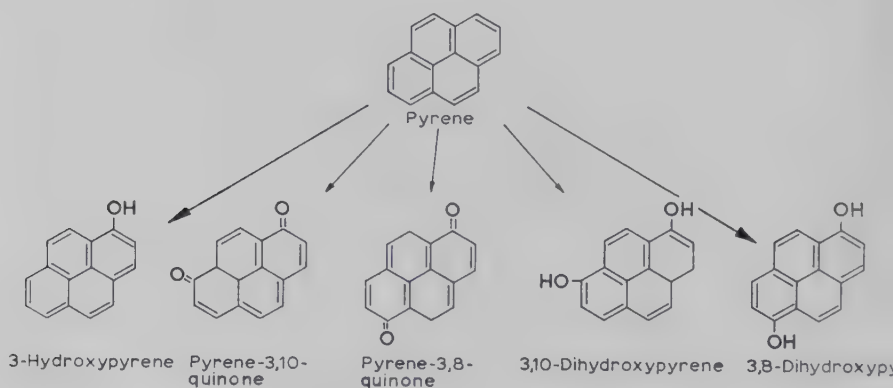
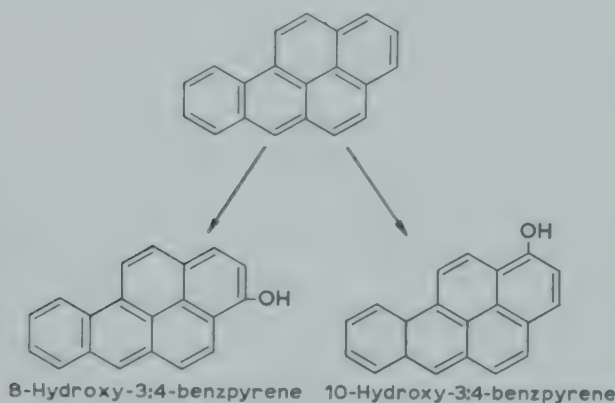


Fig. 85. Biotransformation of pyrene in rats and mice.

(Harper, K. H., 1958).

ene and the 3,10- and the 3,8-quinones have been identified. In the urine the metabolites have been identified as 3-hydroxypyrene, mainly free but possibly conjugated to a small extent, 1- and 3,10-dihydroxypyrenes, mainly conjugated. During passage in the bladder or passage through the cecum and large intestine the glucuronide conjugate of 3-hydroxypyrene is enzymatically hydrolyzed to free phenol. The enzyme effecting this conversion is believed to be β -glucuronidase. The biotransformation of pyrene is shown in Fig. 85.



86. Biotransformation of 3:4-benzpyrene in the rat.

(Young, L., 1950).

In studies on the fate of 3:4-benzpyrene, Berenblum *et al.* (1943, 1946) isolated 8-hydroxy- and 10-hydroxy-3:4-benzpyrene in the feces of rats injected with 3:4-benzpyrene (Fig. 86). Berenblum and Schoental (1943a) isolated 4'-hydroxy-1:2-benzanthracene from the feces of rats and mice injected intraperitoneally with 1:2-benzanthracene. Dickens (1945) concluded that rats convert 9,10-dimethyl-1:2-benzanthracene to 4'-hydroxy-9,10-dimethyl-1:2-benzanthracene. Dobriner *et al.* (1942) isolated 4',8'-dihydroxy-1:2,5:6-dibenzanthracene from the urine of mice and rats after the administration of 1:2,5:6-benzanthracene to these animals. These biotransformations are shown in Fig. 87.

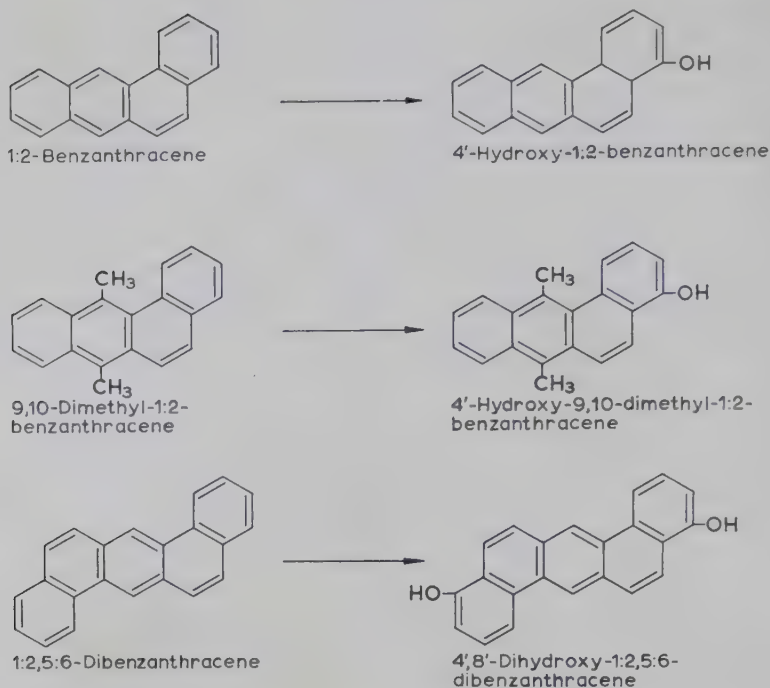


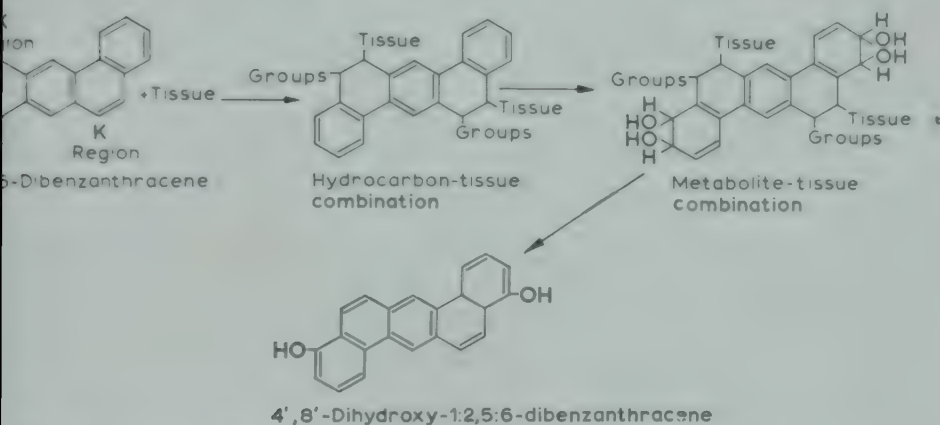
Fig. 87. Biotransformation of 1:2-benzanthracene, 9,10-dimethyl-1:2-benzanthracene and 1:2,5:6-dibenzanthracene in rats and mice.

(Young, L., 19

The non-carcinogenic polycyclic aromatic hydrocarbons, represented by naphthalene, anthracene and phenanthrene, metabolized to a variety of soluble metabolites which are eliminated in the urine. The carcinogenic hydrocarbons, as represented by 1:2-benzanthracene and chrysene (weak carcinogen) and 1:2,5:6-dibenzanthracene, 3:4-benzpyrene and 9,10-dimethyl-1:2-benzanthracene, are metabolized to a variety of excretory products which are found principally in the feces. In addition, the carcinogenic hydrocarbons are excreted principally as unconjugated phenols and quinones (Harper, K. H., 195

Although the mechanism of the carcinogenic activity of polynuclear hydrocarbons is unknown there is evidence to support the idea that carcinogenic activity is related to their metabolism. The water-soluble diols formed from these hydrocarbons

bons combine with tissue constituents in the cells to form a complex which is presumably the cause of the effects which carcinogens produce (Fig. 88). Investigations of the metabolism



88. Hypothetical binding of polycyclic aromatic hydrocarbon and metabolite to tissue. (Boyland, E., 1950).

the carcinogenic hydrocarbons suggest that the carcinogens combine with some tissue constituent through the K-region (high electron density in the 9:10 double bond region) or other reactive group (Boyland E., 1950). The carcinogenic activity of the polycyclic aromatic hydrocarbons may be due to the overall electronic configuration of the molecule (Woermley, 1954) or to combinations of the K-region and the L-region (which corresponds with the *meso* position of anthracene) (Addow, A., 1958). Thus the carcinogenic activity of the polycyclic aromatic hydrocarbons fits into Ehrlich's basic hypothesis: *in vacuo non agunt nisi fixata*. Wiest and Heidelberger (1953) have shown that after topical application of 1:2,5:6-dibenzanthracene ($9:10\text{-}^{14}\text{C}$) to the skin of mice, an irreversible binding occurred between the carcinogen or its metabolite and the nucleoproteins. If the protein combined with the metabolite (key-enzyme, its loss or 'deletion' from the cell would result in profound metabolic changes, which may initiate the neoplastic process.

Threshold limit

A threshold limit has not been established for any carcinogenic polynuclear hydrocarbon for an 8-hour work

The threshold limit for carcinogens should be set at practically zero. Boyland (1958) has suggested that carcinogens differ from other toxic agents in that no safe level exists. The usual relationship of effective doses of drugs in proportion to body weight or surface area may not necessarily hold for carcinogens, because cancer can develop from a few cells or even from a single cell coming in contact with the chemical. If the lesion develops from a single cell or only a few cells, the probability of cancer being produced should be independent of the size of the animal. It may be compared with an infectious disease in which a single cell of a pathogen or a small amount of virus might lead to the death of a large or small animal. In infectious diseases the pathogen multiplies in the host organism. In malignancy, the original cancer cell proliferates. The size of the initial or original proliferative lesion is independent of the size of the host. Thus the same dose of carcinogen would be as effective in a man as in a mouse, ignoring species sensitivity of individual cells.

Fig. 83 shows the dose-response relationships for three polycyclic aromatic hydrocarbons which are carcinogenic for mouse skin. The usual S-shaped dose-response curves are found for 3:4-benzpyrene and methylcholanthrene. The curve for 1:2,3:4-dibenzanthracene passes through the origin. Extrapolation of the data shows that $0.5 \mu\text{g}$ of 1:2,5:6-dibenzanthracene would induce cancer in one mouse out of 500 treated with the hydrocarbon.

Although it appears that there is no safe dose or limit for a carcinogen, it must be emphasized that the results of tests for carcinogenic activity in animals must be considered in relation to the proposed use of the substance (Boyland, E., 1959; Eckardt, R. E., 1959).

Prevention, detection and treatment of exposure

Prevention

The chemist, technician or individual worker handling polycyclic aromatic hydrocarbons in the form of individual chemicals or mixtures should avoid all possible exposures to aerosols or vapors and skin contact with the solids or liquids containing these materials. Special precautions should be taken to avoid exposure to carcinogenic polycyclic aromatic hydrocarbons. In the industrial plant processing large quantities of mineral oils containing carcinogens, engineering controls and industrial hygiene methods should be employed with the objective of avoiding all possible contact.

The cancer control program for high-boiling catalytically cracked oils described by Holt *et al.* (1951) serves as a paragon in the industry. The principal features of this program from the industrial hygiene and preventive standpoint are the following:

- 1. Restrict the number of employees exposed by assigning designated groups of workers to jobs involving contact with the oils.
- 2. Preplacement examination of employees to eliminate individuals who have an excessive number of warts, precancerous lesions, keratoses or other skin diseases.

Employees working with these oils should wear whatever protective clothing is necessary to prevent skin contact. The type of clothing depends on the nature of the job at hand and may include aprons, boots, gloves, or suits. In some refineries protective clothing is colored orange to conform with the general practice of identification of carcinogenic oils.

Identification of equipment containing the oils by labeling storage containers and cautioning against contact with the contents. In some plants all lines, tanks and other pieces of equipment containing the oils are painted orange for identification and oil drums going to laboratories for analysis or equipment parts going to repair shops are identified with an orange label. Signs are located in areas where contact with these oils may occur. Reduce points of exposure to a minimum by limiting the

places where employees are exposed to physical contact reducing the number of lines, tanks, etc.

6. Employee education and personal hygiene are also stressed. Individuals working with the carcinogenic oils are informed of the hazards associated with contact with these materials. The distribution of booklets through the medical department is required. If skin contact with the oils has occurred, the skin should be washed promptly with soap and water. All employees in the program are encouraged to wear clean underwear and work clothes daily, and are required to take a shower before leaving the plant. Where exposure is unavoidably excessive, the clean clothing and shower programs are compulsory.

(B) Detection

There is no established biochemical test to determine if exposure to polycyclic aromatic hydrocarbons has occurred. It is necessary to ascertain if subclinical or incipient injury exists as a result of contact with these hydrocarbons.

Periodic health examinations should be conducted regularly on individuals working with carcinogenic oils or carcinogenic polycyclic aromatic hydrocarbons. The health examination should consist of a brief interval history and complete physical examination with special attention directed to the presence of warts, papillomas, tumors, dermatitis or other abnormalities of the skin. If an employee has warts or precancerous lesions on the surface of the body, he should be permanently removed from work in which he might again be exposed to carcinogenic hydrocarbons.

(C) Treatment

Any employee working with carcinogenic hydrocarbons who has a wart, a precancerous or cancerous lesion on the surface of the body should have prompt treatment. This consists of surgical excision *in toto*. The diagnosis should be made on the excised tissue by histological examination. The worker should be re-examined at regular intervals until the physician is reasonably certain that there is no evidence of recurrence.

Aromatic hydrocarbon mixtures: solvents, fuels and lubricants

Although individual aromatic hydrocarbons are used in industry for numerous specific applications, the 'life-blood of industry' consists of complex mixtures of hydrocarbons used as solvents, fuels, and lubricants. Aromatic hydrocarbons in considerable concentrations may be important essential components of these mixtures or may be present in minor quantities as contaminants and impurities.

Some idea of the toxicity and health hazards associated with the use of these mixtures may be obtained from their qualitative and quantitative chemical composition and knowledge of the toxicity of the individual constituents. It must be emphasized that one can make only a 'qualitative' estimate of the toxicity of a chemical mixture based on the chemical composition and toxicity of the individual ingredients in a mixture. The well recognized phenomenon of synergism is unpredictable and not easily amenable to mathematical treatment. There is only one way to determine the toxicity of a chemical mixture and that is to do the actual experiment.

SOLVENTS

From the standpoint of toxicity and hazard to health it is important to know if a solvent or commercial mixture contains benzene in any significant concentration. Benzene is unquestionably the most dangerous hydrocarbon used in industry. Examination of the early studies describing the health hazards

associated with the use of toluene and the xylenes in industry reveals that these solvents contained considerable amounts of benzene as a contaminant. It thus appears that many of the effects described, particularly on the hemopoietic tissue, are in all probability due to benzene. Because of the ubiquitous presence of benzene, particularly in aromatic solvents, and its insidious chronic toxicity, it is important to know the concentrations of benzene in commercial hydrocarbon mixtures.

Benzene has been found to be a contaminant of 'non-aromatic' solvents which would not be expected to contain benzene according to the physical properties and information supplied by the manufacturer. Some states in the U.S.A. require labeling of products containing more than 1 % benzene. If the benzene content exceeds 1 % the supplier is in violation of the law if he fails to provide a warning label.

Elkins and Pagnotto (1956) found benzene ranging from 0.5 to 7 % in 8 samples of petroleum naphtha solvents analyzed. These authors believe that the ordinary use of these solvents containing 1 to 2 % benzene by volume would not produce benzene vapor hazards. It is conceivable, however, that serious benzene exposure could result from the use of solvents containing 5 % benzene in some applications, such as fabric spreading, spraying, and similar operations. In the air in one plant where hexane with a relatively low benzene content (1.5 %) was used as a solvent in a fabric spreading operation, a benzene vapor concentration of 1 p.p.m. was found. The concentration of naphtha vapor in this plant was 200 p.p.m. as determined by the combustible gas indicator.

Hydrocarbon solvents are commonly classified according to the principal classes of hydrocarbons contained in the mixture: aliphatic, naphthenic (cycloparaffinic) or aromatic. The two broad categories are aliphatic and aromatic. A hydrocarbon mixture containing 49.3 % aromatics is classified with the series of aliphatic hydrocarbon solvents in a Handbook of Solvents (Mellan, I., 1957). Although this represents an extreme case

of the aliphatic solvents listed contained from 1 to 10% aromatic hydrocarbons. These solvents included petroleum, aliphatic naphtha, mixed and normal hexanes, textile solvents, VM&P naphtha, heptane, solvent naphtha, Varsol^R, turpentine spirits, Stoddard solvent and petroleum spirits. As discussed above, from the standpoint of health hazard and toxicity it is important to know how much benzene is present rather than the total aromatic content.

There are numerous commercial hydrocarbon mixtures designated as aromatic hydrocarbon solvents. These solvents may consist of many individual hydrocarbons which are principally derivatives of benzene, indane and naphthalene. They are extensively used as solvents for paints, plastics, pesticides and protective coatings and as substitutes for benzene. The variety of individual hydrocarbons in commercial aromatic hydrocarbon solvents is illustrated by the component analysis of Solvesso^R 100 and Solvesso^R 150 shown in Tables 52 and

TABLE 52

COMPOSITION OF AROMATIC HYDROCARBONS IN SOLVESSO 100*

<i>Hydrocarbon</i>	<i>Vol. % of solvent</i>
n-Butylbenzene	0.00
sec-Butylbenzene	0.00
tert-Butylbenzene	0.00
1,2-Diethylbenzene	0.00
1,3-Diethylbenzene	0.00
1,4-Diethylbenzene	0.00
1,2-Dimethyl-3-ethylbenzene	0.09
1,2-Dimethyl-4-ethylbenzene	0.34
1,3-Dimethyl-2-ethylbenzene	0.07
1,3-Dimethyl-4-ethylbenzene	0.23
1,3-Dimethyl-5-ethylbenzene	0.40
1,4-Dimethyl-2-ethylbenzene	0.14

1,2-Dimethylbenzene	0.6
1,3-Dimethylbenzene	0.2
1,4-Dimethylbenzene	0.1
Ethylbenzene	0.0
Indane	1.8
Isobutylbenzene	0.3
Isopropylbenzene	0.5
1-Methyl-2-ethylbenzene (<i>o</i> -Ethyltoluene)	8.4
1-Methyl-3-ethylbenzene (<i>m</i> -Ethyltoluene)	16.0
1-Methyl-4-ethylbenzene (<i>p</i> -Ethyltoluene)	7.9
1-Methyl-2-isopropylbenzene	0.0
1-Methyl-3-isopropylbenzene	0.4
1-Methyl-4-isopropylbenzene	0.1
1-Methyl-2- <i>n</i> -propylbenzene	0.0
1-Methyl-3- <i>n</i> -propylbenzene	
1-Methyl-4- <i>n</i> -propylbenzene	0.0
1-Methylindane	0.0
2-Methylindane	0.0
4-Methylindane	0.0
5-Methylindane	0.0
<i>n</i> -Propylbenzene	4.7
1,2,3,4-Tetramethylbenzene	0.1
1,2,3,5-Tetramethylbenzene	0.4
1,2,4,5-Tetramethylbenzene	0.3
Toluene	0.0
1,2,3-Trimethylbenzene (Hemimellitene)	7.5
1,2,4-Trimethylbenzene (Pseudocumene)	38.0
1,3,5-Trimethylbenzene (Mesitylene)	7.0
C ₁₁ -aromatics	0.0
Aromatics	Total 96.45

* Courtesy Esso Standard Oil Company, New York, N. Y., U.S.A.

The name 'naphtha' is applied to distillates from petroleum and to various grades of light oils obtained in the distillation of coal tar. The term is applied to aliphatic and aromatic hydrocarbon mixtures having a great diversity of chemical compositions. A variety of naphthas available commercially

TABLE 53

COMPOSITION OF AROMATIC HYDROCARBONS IN SOLVESSO 150*

<i>Hydrocarbon</i>	<i>Vol % of solvent</i>
<i>n</i> -Butylbenzene	2.47
<i>sec</i> -Butylbenzene	0.08
<i>tert</i> -Butylbenzene	0.05
<i>m</i> -Cymene	0.13
<i>o</i> -Cymene	0.01
<i>p</i> -Cymene	0.52
1,2-Diethylbenzene	1.72
1,3-Diethylbenzene	1.10
1,4-Diethylbenzene	0.56
1,2-Dimethyl-3-ethylbenzene	2.86
1,2-Dimethyl-4-ethylbenzene	6.64
1,3-Dimethyl-2-ethylbenzene	0.71
1,3-Dimethyl-4-ethylbenzene	4.17
1,3-Dimethyl-5-ethylbenzene	2.80
1,4-Dimethyl-2-ethylbenzene	3.26
<i>m</i> -Ethyltoluene	0.37
<i>o</i> -Ethyltoluene	0.02
<i>p</i> -Ethyltoluene	0.01
Indane	0.46
Isobutylbenzene	0.32
Isopropylbenzene	0.01
1-Methyl-3- <i>t</i> -butylbenzene	0.76
1-Methyl-2- <i>n</i> -propylbenzene	1.26
1-Methyl-3- <i>n</i> -propylbenzene	2.08
1-Methyl-4- <i>n</i> -propylbenzene	1.93
1-Methylindane	0.91
2-Methylindane	2.43
4-Methylindane	9.28
5-Methylindane	2.02
Naphthalene	4.03
<i>n</i> -Propylbenzene	0.00
1,2,3,4-Tetramethylbenzene	3.66
1,2,3,5-Tetramethylbenzene	8.84

1,2,4,5-Tetramethylbenzene	5.53
Toluene	0.02
1,2,3-Trimethylbenzene	0.10
1,2,4-Trimethylbenzene	0.05
1,3,5-Trimethylbenzene	0.01
<i>m</i> -Xylene	0.05
<i>o</i> -Xylene	0.03
<i>p</i> -Xylene	0.03
C ₁₁ -Naphthalenes	0.31
C ₁₁ -Indanes	3.58
C ₁₁ -Alkylbenzene	18.27
C ₁₂ -Alkylbenzene	0.73
C ₁₂ -Indanes	0.08
C ₁₃ -Alkylbenzene	0.02
C ₁₀ -Indenes	0.10
C ₁₁ -Indenes	0.07
C ₁₂ -Naphthalenes	} Trace
C ₁₃ -Naphthalenes	
C ₁₂ -Indenes	
Aromatics	Total 94.55

* Courtesy Esso Standard Oil Company, New York, N. Y., U.S.A.

are described by the terms, coal-tar naphtha, petroleum naphtha, high flash naphtha, solvent naphtha, aromatic solvent naphtha, heavy aromatic naphtha, etc. From the standpoint of toxicity it is important to make a distinction between 'coal-tar naphtha' and 'petroleum naphtha'. 'Coal tar naphtha' is an aromatic solvent consisting principally of a mixture of toluene, xylene and cumene. If a sample of coal-tar naphtha has a low boiling point it may contain appreciable amounts of benzene. 'Petroleum naphtha' consists principally of a mixture of paraffin hydrocarbons somewhat higher in molecular weight than paraffin hydrocarbons in gasoline (hexanes, heptanes, octanes). The composition of the aromatic fraction of a virgin petroleum naphtha is shown in Table 54. Other petroleum

TABLE 54

AROMATIC HYDROCARBONS IN VIRGIN PETROLEUM NAPHTHA*

<i>Hydrocarbon</i>	<i>Vol % of naphtha</i>
Monocyclic derivatives of benzene	
Benzene	0.21
Toluene	2.32
Ethylbenzene	1.07
<i>o</i> -Xylene	1.20
<i>m</i> -Xylene	2.30
<i>p</i> -Xylene	0.84
Isopropylbenzene	0.18
Methylethylbenzenes	0.96
Trimethylbenzenes	4.98
$C_6H_5-C_4H_9$	3.90
$C_6H_5-C_5H_{11}$	1.78
$C_6H_5-C_6H_{13}$	0.56
$C_6H_5-C_7H_{15}$	0.052
Alkenyl benzenes and/or cycloparaffin-aromatics	
$C_6H_5-C_3H_5$	0.27
$C_6H_5-C_4H_7$	0.66
$C_6H_5-C_5H_9$	0.92
$C_6H_5-C_6H_{11}$	0.32
$C_6H_5-C_7H_{13}$	0.027
Dicyclics	
Dicyclic	1.3

*After Mellan, I. (1957).

s falling in the naphtha boiling range may be principally naphthalenic.

The toxicological and pharmacological properties of 'coal-tar naphtha' (free from benzene) are similar qualitatively to the naphtha produced by toluene, cumene and the xylenes. Since the principal effect of these aromatic hydrocarbons is central ner-

vous system depression, in this instance the toxicity of the ponents appears to be additive.

The threshold limit for 'coal-tar naphtha' established by the American Conference of Governmental Industrial Hygienists is 200 p.p.m. for an 8-hour work day.

Heavy Aromatic Naphtha (HAN)^R is a selected aromatic fraction naturally occurring in petroleum which has a boiling range of 328° F to 540° F. Because of its low phytotoxicity it is used as a solvent for pesticide formulations applied to fruits and vegetables. It contains approximately 85% of aromatic hydrocarbons by volume, which are principally indenes, naphthalenes and diphenyls. The toxicity of Heavy Aromatic Naphtha has been investigated by Kehoe and Nelson (Nelson, F. and Fiero, G., 1954). The studies involved the intermittent exposure of experimental animals to low pressure aerosols of the solvent and human patch testing. A low degree of toxicity was indicated by these short-term intermittent exposure tests. In the patch-testing of 100 human subjects a significant degree of primary skin irritation was found. Subsequent exposure of the test sites to ultraviolet light produced a mild intensification of the skin reactions in five of the subjects tested with Heavy Aromatic Naphtha^R. Four of these reactions subsided after 3 hours. In the fifth subject the reaction persisted for 6 hours. These cutaneous reactions did not differ significantly from the reactions observed with a commonly used pesticide solvent as the control. It was concluded that neither solvent induced a significant degree of skin irritation or photosensitization.

FUELS

(A) Gasolines-Petrol

Gasolines or petrols are complex mixtures of paraffinic, naphthenic (cycloparaffinic) and aromatic hydrocarbons, which fall approximately in the C₄ to C₁₁ range and boil over a range of less than 100° F to somewhat over 400° F. Widely varying

ants of individual constituents are contained in typical line blends, depending upon such factors as origin of the refining streams, seasonal requirements and intended use. 'Straight run' gasoline made from petroleum produced in the U.S.A. is principally paraffinic in character although several refineries in the western part of the country yield straight run gasolines which are much more aromatic. Many foreign crude oils yield highly aromatic gasolines, notably Borneo petroleum. Only 40% of the hydrocarbons present in the gasoline fraction from Borneo crude are aromatic. These aromatic hydrocarbons are principally benzene, toluene and xylenes. The development of catalytic cracking has made it possible

TABLE 55
COMPOSITION OF AROMATIC HYDROCARBONS IN CATALYTICALLY
CRACKED GASOLINE (BOILING RANGE 35 TO 218 °C)*

<i>Hydrocarbon</i>	<i>% by volume of gasoline</i>
Alkylbenzenes from $C_6H_5.C_3H_7$ to $C_6H_5.C_7H_{13}$	2.177
Alkylbenzenes	1.78
Benzene	0.21
Alkylbenzenes	3.90
Cyclic aromatics	1.3
Alkylbenzene	1.07
Alkylbenzenes	0.052
Alkylbenzenes	0.56
Propylbenzene	0.18
Ethylethylbenzenes	0.96
Propylbenzene	0.16
Benzene	2.32
Ethylbenzenes	4.98
Xylene	2.30
Xylene	1.20
Xylene	0.84

after Brooks, B. T. *et al.* (1955).

to produce high yields of gasoline from higher boiling petroleum fractions. Within the last few years there has been a revolution in the methods of gasoline manufacturing. Catalytic reforming (see p. 15) which converts cycloparaffins to aromatics is replacing thermal reforming. This has resulted in an increased concentration of aromatic hydrocarbons in automotive and aviation gasolines. The composition of the aromatic hydrocarbon fraction of a catalytically cracked gasoline is shown in Table 55.

'Motor benzol' is a product derived from coal tar which contains principally benzene (approximately 70%) toluene and xylene. It has been used as a component of gasoline particularly in England and in Europe but also in the U.S.A. for many years. The German Dynalkol contained 70% gasoline blended with alcohol and benzene. Dynax motor fuel for speed boats is a methanol-benzene blend.

There is no evidence that a public health hazard is associated with the proper use of these benzene-containing motor fuels. Because of their high benzene content these fuels must be handled with all the precautions necessary for minimizing exposure to benzene (see p. 104).

(B) *Kerosine (kerosene, coal-oil, range oil, No. 1 heating oil)*

Kerosine is a complex mixture of aliphatic, olefinic, naphthenic (cycloparaffinic) and aromatic hydrocarbons boiling in the range of 340°-560° F (171-293° C). Individual kerosine compositions vary widely depending on source, but generally aliphatic hydrocarbons in the C₉-C₁₆ range predominate. Kerosines normally contain from 15 to 20% aromatic hydrocarbons by volume and rarely more than 25%. The composition of aromatic hydrocarbons according to molecular types for kerosine containing approximately 20% aromatics is shown in Table 56.

Kerosine is employed for illuminating and heating purposes as a constituent of fuels for internal combustion engines, 'turbo-prop' and jet aircraft engines. Range oil is the heaviest kerosine

TABLE 56

COMPOSITION OF AROMATIC HYDROCARBONS IN KEROSENE*

<i>Aromatic ring type</i>	<i>% by volume in aromatic fraction</i>
Monocyclic	6
Benzene	22
Alkenes	7
Phenyls	11
1-Methylnaphthalene	} 54
2-Methylnaphthalene	
Acenaphthalin (1,2,3,4-Tetrahydronaphthalene)	

*after Rossini, F. D. *et al.* (1954).

illate which is sufficiently volatile to burn freely in the wick heating range, but not so volatile as to be explosive. Deodorized kerosine (*e.g.* Deobase) is highly refined by treatment with activated carbon or by clay filtration. It is commonly used in insect sprays.

Kerosine ingestion is one of the leading causes of accidental poisoning in children in the U.S.A. The children develop a

TABLE 57

ORAL TOXICITY OF KEROSENE COMPARED
WITH OTHER COMMON LIQUID CHEMICALS*

<i>Chemical</i>	<i>LD-50 mg/kg</i>	<i>Animal</i>	<i>Toxicity class</i>
Acetic acid	3,310	rat	Slightly toxic
Formic acid	3,730	rat	Slightly toxic
Propyl alcohol	5,840	rat	Practically non-toxic
Ethyl acetone	9,750	rat	Practically non-toxic
Butyl alcohol	13,660	rat	Practically non-toxic
Glucose	27,000	rabbit	Relatively harmless
Kerosine	28,350	rabbit	Relatively harmless

*Compiled from Spector, W. S. (1956).

chemical pneumonitis due to aspiration of kerosine rather than absorption of hydrocarbons from the gastrointestinal tract after ingestion. Kerosine has a low order of toxicity by the oral route as shown in Table 57. The toxicity of kerosine by direct aspiration is approximately 150 times greater than the toxicity by the oral route (Gerarde, H. W., 1959a).

(C) *Jet fuels*

Commercial aviation jet fuels, JP-1, JP-3, and JP-5 are essentially kerosines varying in aromatic hydrocarbon concentration from 10 to 20% by volume. Military jet craft use a wide range of fuel consisting of 30% kerosine and 70% gasoline because they operate in lower temperatures than commercial airliners. The individual aromatic hydrocarbons found in jet fuels are listed in Table 55 and 56 which give the aromatic hydrocarbon components for gasoline and kerosine respectively.

(D) *Diesel fuels*

In general, paraffinic stocks are by far the best diesel fuels from the standpoint of ignition quality. Fuels with a high aromatic content are the poorest, with olefinic and naphth

TABLE 58
AROMATIC HYDROCARBONS TYPES IN DOMESTIC HEATING OIL
(NO. 2 FUEL OIL) AND DIESEL FUEL*

<i>Hydrocarbon type</i>	<i>Vol % of total (approx.)</i>
Alkylbenzenes	4.1
Indanes and tetralins	3.7
Dinaphthene benzenes	1.7
Alkyl naphthalenes	9.1
Acenaphthenes	4.0
Acenaphthylenes	3.4
Phenanthrenes	2.7

* Courtesy Esso Research and Engineering Company, U.S.A.

(cycloparaffinic) fuels being intermediate. Straight-run fuels cut directly from the crude oil by distillation are superior to cracked cycle stocks from the same base crude. The aromatic hydrocarbon content of a typical diesel fuel ranges from 30 to 35 %. The principal aromatic hydrocarbon types and the amounts present are shown in Table 58. Toxicologically and pharmacologically the diesel fuels are similar to kerosine.

Fuel oils

Fuel oils are normally consumed in burners to produce heat distinguished from gasoline, jet fuels and diesel fuels used in combustion engines. The liquid burner fuels are classified as *distillate* fuels or *residual* fuels. A distillate fuel is that portion of the original petroleum which was vaporized and condensed as a liquid. A residual fuel is that portion which is not vaporized in heating but is withdrawn from the still in liquid form. The lightest and most volatile of the liquid burner fuels is kerosine (see Section B) which is designated as No. 1 Fuel oil or kerosene.

Domestic heating oil (No. 2 Fuel Oil) is the product used in domestic household heating burners. The raw materials from which it is made are derived from crude oil by means of straight distillation, thermal and catalytic cracking. The product is subjected to substantially the same processing steps used in gasoline manufacture, including final clay filtration. The boiling range of a typical No. 2 Fuel oil is from 350° F to 650° F. It consists of paraffins (37-43 %) cycloparaffins or naphthenes (32 %) and aromatics (30-32 %). The aromatic hydrocarbon types and the amount present are shown in Table 58. Toxicologically it can be compared with kerosine.

Residual fuels may be considered as a blend of the various residual and lighter diluent oils in the refinery having a boiling range from approximately 400° F up to and including the heaviest liquids in the crude oil or produced by refinery processes. The residual fuels in the No. 6 fuel oil classification (Bunker

C Fuel) are high in viscosity and require warming before they can be pumped and burned properly. There are numerous grades of residual fuels for a wide variety of uses including steam generation, commercial heating, manufacturing processes, and propulsion for ocean liners.

High-boiling petroleum products such as residual fuel oil may contain thousands (if not millions) of types of hydrocarbon derivatives and isomers of varying complexity. Certain petroleum oils which are obtained from severe cracking processes

TABLE 59
AROMATIC HYDROCARBONS IN CRACKED TAR*

<i>Boiling range, °F</i>	<i>Weight % of distilled fraction</i>	<i>Probable or actual hydrocarbons present</i>
392-441	5.3	Naphthalene
441-482	6.7	Methylnaphthalenes
482-518	8.3	Dimethyl- and ethyl- naphthalenes
518-554	8.3	{ Acenaphthene** Trimethyl- and dimethyl- ethylnaphthalenes
554-608	14.4	{ Fluorene** Naphthalene homologs (C ₁₄ -C ₂₀)
608-680	30.1	{ Anthracene** Phenanthrene
680-716	14.7	{ Methyl-, dimethyl- and ethylantracenes and phenanthracenes
	12.2	{ Pyrene** Fluoranthene Higher homologs of anthracene and phenanthrene

* After Fischer, H. G. M. *et al.* (1951).

** Isolated and identified.

contain material boiling above 700° F have been shown to be carcinogenic for mice, rabbits and monkeys (Holt, J. *et al.*, 1951). The activity is associated with the fraction containing cyclic aromatic hydrocarbons. It must be emphasized that kerosenes, home heating oils and related products are not carcinogenic even though they contain aromatic hydrocarbons. Many of the high-boiling products are inactive unless the conditions of synthesis or processing (e.g. catalytic cracking) have favored the production of highly condensed aromatic components (Schroeder, H. G. M. *et al.*, 1951).

The aromatic hydrocarbons isolated and identified in a fraction of severely cracked tar are shown in Table 59.

LUBRICANTS

The lubricating oil fractions from crude oils are complex mixtures, of straight and branched chain paraffinic, naphthenic (cycloparaffinic) aromatic and polycyclic aromatic hydrocarbons which fall approximately in the C₁₇ and higher range. The boiling points range from 575° to 1500° F depending on the source. Thousands of different hydrocarbon compounds are believed to exist in these lubricating oil mixtures the uses of which range from industrial lubricants to medicinal mineral oils. Among the more common lubricants used in industry are engine oils, hydraulic oils, process oils, gear oils and greases. A mass spectrometric analysis of seven medium-viscosity lubricating oils from various crudes was recently reported by André and O'Neal (1959). The principal components of the aromatic fraction were monoaromatics which ranged from 6 to 10.5 vol % of the lubricating oils. Smaller percentages of di-, tri and tetra-aromatics were also found. The aromatic hydrocarbon molecular types identified in this study are shown in Fig. 89.

Lubricating oils and greases have a low order of toxicity when taken internally. The prolonged inhalation of mists or

vapors in high concentrations may cause mucous membrane irritation and chemical pneumonitis. The aspiration of medium viscosity mineral oil is known to cause a chronic chemical pneumonitis called 'lipoid pneumonia'.

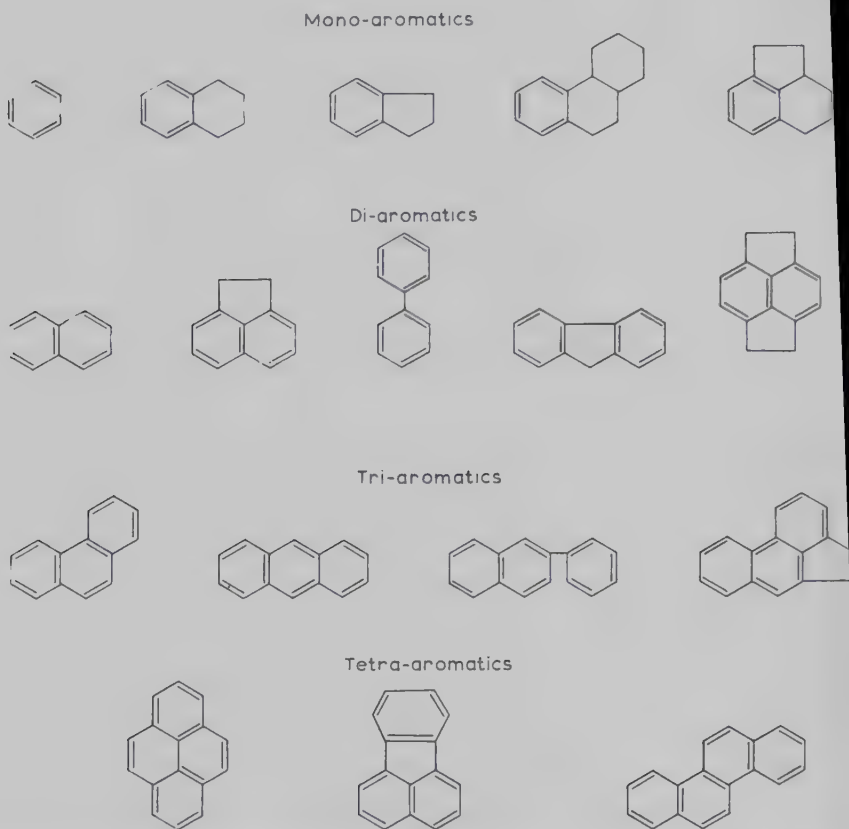


Fig. 89. Aromatic hydrocarbon types in medium viscosity lubricating oils.
(André, M. L. and O'Neal, M. J., Jr., 1954)

Frequent, prolonged contact with lubricating oils may cause contact dermatitis. This is characterized by an acne-type lesion on the hands, forearms and thighs—oil folliculitis. It is not known what fraction of the lubricating oils is responsible for these cutaneous effects.

Although lubricating oils contain polycyclic aromatic hydrocarbons, they show little if any activity as carcinogens by

ed topical application to the skin of mice. As stated in the
on on Fuel Oils, carcinogenic activity is associated with
natic oils derived from catalytic or severe thermal cracking
ng above 700 ° F. Cases of human skin cancer have resulted
a prolonged contact with unrefined waxes and cutting oils.
carcinogenic activity of certain polynuclear hydrocarbons
scussed further in Chapter 12.

Appendix

SELECTED GLOSSARY OF TERMS USED IN THE PETROLEUM INDUSTRY*

Acid treating

An oil-refining process in which unfinished petroleum products such as gasoline, kerosine, diesel fuel, and lubricating stocks, contacted with sulfuric acid to improve color, odor, and other properties.

Alkylate

The desired product obtained in the alkylation process. In the butene alkylation process the product is principally C⁸-isomers.

Alkylation

The addition reaction of olefins and iso-paraffins, particularly the union of butenes and isobutane, using a catalyst at low temperature to produce a saturated compound of high octane number.

Aromatic

Organic compounds which contain one or more benzene rings.

Aromatic index

A figure calculated from viscosity and gravity or other inspection data on gas oils. It is indicative of the aromatic content and cracking value of the oil. Aromatic stocks are hard to crack.

* Compiled from Esso Research and Engineering Company Booklet, 1954.

Asphalt

Dark to dark-brown, solid or semi-solid cementitious material which usually liquifies when heated. The predominating constituents are bitumens, which occur in nature or are obtained as residue by refining petroleum.

Asphalt base crude

Crude whose highest boiling fractions are asphaltic in nature.

Asphalt, blown

Asphalt produced from asphaltic residuals through agitation with heated air at high temperature. The oxidizing action of the heated air produces a much more viscous asphalt product, whose consistency is affected by temperature changes than is natural asphalt.

Asphaltenes

Components of the bitumen in petroleum which are soluble in carbon disulfide but insoluble in paraffin naphthas.

Base stock

Primary petroleum fraction from which a specification product is prepared by adding other components to it.

Benzene

Colorless, flammable, volatile liquid obtained from petroleum. It consists of a mixture of hydrocarbons, and is totally distinct from the aromatic hydrocarbon 'benzene'.

Bitumen

Generic term applied to native substances of variable color, hardness and volatility. Any mixture of high boiling hydrocarbons which is soluble in carbon disulfide. Bitumen includes asphalts, coal tar, and pitch.

Bottoms

Residue remaining in a distillation unit after the highest boiling material to be distilled has been removed. The boiling range of the

bottoms will depend on the feed stock to the still and the amount of material distilled off.

Bright stock

High-viscosity lubricating oils which have been refined to make clean products of good color.

Cantona

A trade name for filtered steam cylinder oils of excellent quality. They atomize readily and separate easily from condensate.

Casing-head gasoline

The volatile but condensable constituents obtained from natural gas or from the gas given off by the oil well at the top, or head, of a casing.

Cetane number

A means of expressing the ignition quality of a diesel fuel. It is defined as the percentage by volume of cetane in a mixture of cetane and methyl naphthalene which has the same ignition quality in an engine as the fuel under test. High cetane number indicates good diesel fuel.

Clarified oil

The heavy oil from the bottom of the fractionator in a catalytic cracking process from which the catalyst fines have been removed by settling.

C-oil

A heavy bodied sticky, almost colorless liquid made by polymerization of butadiene and styrene. It is used in paints.

Cracking

The process of breaking up heavy petroleum products into lighter products such as gas and gasoline. This may be accomplished by use of heat, pressure, and/or catalysts.

Cut

(See Fraction.)

back asphalt

Asphalt which has been rendered liquid for easier handling by fluxing with a volatile product such as naphtha. Upon exposure to the atmosphere, the volatile product evaporates leaving the asphalt.

back products

Petroleum or tar residuals which have been fluxed or diluted, each with its own or similar distillates.

base gas oil

Gas oil boiling in the same range as the feedstock which is condensed from the reactor product and recycled to a cracking unit.

base stock

Product taken from a later stage of a process and recharged to the process at an earlier stage.

basephalting

A process for removing asphalt from reduced crude which utilizes the solubility of non-asphaltic compounds in liquid propane to make the separation. Asphalt is insoluble in propane or butane.

base index

A product of the A.P.I. gravity and aniline point (in degrees Fahrenheit) of a diesel fuel, divided by 100. It is an indication of ignition quality of the fuel and is empirically related to cetane number.

base gas

A low boiling petroleum hydrocarbon gas (usually C_1 , C_2 , and C_3) which has been passed through the gas absorption equipment. It is distinguished from 'wet' gas which contains condensable material such as light naphtha.

baseified asphalt

An emulsion of asphalt cement and water containing a small amount of an emulsifier.

Engler distillation

A standard test for determining the volatility characteristics of gasoline by measuring the per cent distilled at various specified temperatures.

Feed stock

Crude oil or a fraction therefrom to be charged to any process equipment.

Flash point

The lowest temperature at which an oil or fuel gives off sufficient vapor to form a mixture which will ignite, under standard test conditions.

Fluid catalytic cracking

A process for cracking gas oils which uses a fluid solids catalyst. When mixed with a moving stream of vapors, the catalyst assumes many properties of a fluid.

Flux stock

A petroleum stock such as naphtha which is used to dilute a heavy residual stock so it can be handled as a liquid.

Fraction

A portion or cut of a petroleum product usually produced by distillation. It may have any boiling range narrower than the crude oil from which it came.

Fresh feed

Crude petroleum or petroleum distillate which is being fed to a particular process unit for the first time.

Gas oil

Any distillate process stock heavier than naphtha obtained during fractionation of crude. The stock may have an initial boiling point as low as 400° F. It is called 'light' or 'heavy' depending on its final boiling point.

oline

efined petroleum product which is suitable for use as a fuel in
nal combustion engines.

ase

semi-solid lubricant consisting essentially of a mixture of mineral
and soap. The properties of the material depend on the type of
and the viscosity and other properties of the mineral oil.

a

ubber-like, sticky deposit, black or dark brown in color, which
ults from the oxidation of lubricating oils in service and from
table constituents in gasoline which deposit during storage or use.

rtcut

enerally, the portion of catalytic cracking cycle stock boiling in the
e range as the fresh feed.

ting oil

etroleum distillate boiling between about 450° and 650° F and
ing a minimum °API gravity of 30.

vy ends

higher boiling fraction of a product, especially of gasoline. The
n is general and is used differently by different people.

rofining

catalytic treating process carried out in the presence of hydrogen
at lower temperature than hydroforming. This process is a net
sumer of hydrogen. It is used for treating naphtha, heating oil,
e oil, and kerosine in place of acid treating. It removes sulfur and
irates olefins and diolefins.

roforming

catalytic reforming of naphtha at elevated pressures and tempera-
s in the presence of hydrogen. This process is a net producer of
rogen and is used in place of thermal reforming. Either a fluid or
d bed catalyst system may be used.

Hydroskimming

A refinery operation which upgrades only the gasoline in the crude oil by reforming. It is done in refineries where the demand for gasoline is too low to justify catalytic cracking.

Hyperflow process

Trade name of a process developed by the Union Oil Company which uses a 'moving bed' of catalyst. The catalyst in the form of small beads ($1/16''$ – $1/8''$ dia.), flows down through the reactor and is carried back to the top through an external transfer line by pressure gas.

Iso-octane

The common name for 2,2,4-trimethylpentane. It has a rating of 100 octane number by definition. It is the primary reference fuel in knock rating.

Lean oil

The stripped menstuum in the operation of an absorption tower. When the menstuum is fed to the tower in which the gas is to be stripped, it is 'lean oil'. After it absorbs the heavy ends from the gas, it is 'fat oil'. The fat oil is stripped of these heavy ends and is again lean oil.

Light ends

The low boiling portion of a petroleum fraction, generally pentane and lighter compounds.

Light naphtha

One of the lower boiling gasoline components; usually those which are 95% off at or below 200° F.

Mahogany acids

The oil-soluble petroleum sulfonic acids remaining dissolved in the oil when, in the manufacture of white oils with fuming acid, the acid sludge has been settled and drawn off.

Microcrystalline wax

Microcrystalline, high melting point petroleum wax obtained by removing the wax component of the oil from petrolatum.

Boiling point

Temperature approximately equal to the point at which 50 % of a material is distilled. There are, however, several specific definitions of the term boiling point and the term should be used only with a clear understanding of its meaning in the context.

Bottoms distillates

Distillates obtained between kerosine and lubricating oil fractions in the refining processes. These include light fuel oils and diesel fuel.

Crude oil

Oil derived from a mineral source such as petroleum, shale or tar sands.

Crude oil

General term applied to low boiling liquid petroleum products and heavy products of natural gas.

Crude oil

Weight % of total carbon atoms actually in naphthene ring structures in a petroleum oil.

Crude oil

(Casing-head gasoline.)

Crude oils

Lubricating oils, prepared without chemical treatment. They derive their name from the fact that they have not been treated with either acid or alkali, but have been purified by filtration.

Octane number

Number indicating the relative anti-knock quality of a gasoline determined upon a comparison with the reference fuels iso-octane (100) and normal heptane (0).

octane number) and normal heptane (0 octane number). The octane number of an unknown fuel is the % volume of iso-octane and normal heptane which matches the unknown fuel in knocking tendencies under a specified set of conditions. There are several different octane number tests, *e.g.* research, motor, road, which are made under different test conditions.

On-stream

Term used in the industry to denote a plant or unit in operation.

Once-through

A continuous process in which no portion of the product is recycled.

Oxidized asphalt

(See Asphalt, blown.)

Paraffin base

Usually a crude which has a high per cent of paraffin hydrocarbons and essentially no asphaltenes in the residual fractions.

Paraffin wax (as a finished product)

Wax of very low oil content, highly refined, white, with some degree of translucency, almost tasteless and odorless.

Petrolatum

A soft, salve-like material obtained from petroleum oils, and consisting essentially of micro-crystalline waxes in association with substantial quantities of oil. It may vary in color from white to dark brown.

Petroleum

A liquid material occurring naturally in the earth and consisting essentially of solid, liquid and gaseous hydrocarbons.

Pipe still

A primary distillation unit for petroleum oils used to separate various components having different boiling points. It consists essentially of a furnace and a fractionating tower with access equipment.

h
orm, loosely used, which usually denotes the residuum from the
llation of crude petroleum, natural asphalts, coal-tar, etc. A
in product. (See Tar.)

forming

fixed bed catalytic reforming process employing a platinum
lyst developed by Universal Oil Products Company.

erforming

fixed bed catalytic reforming process employing a platinum
lyst developed by Esso Research and Engineering Company.

ne cut naphtha

petroleum solvent whose gravity varies from 68° to 73° A.P.I.
first cut in crude petroleum distillation is still called the 'P.C.
htha.'

ne fuel products

fers to petroleum products as differentiated from chemical pro-
ts.

ench oil

d oil injected into the product leaving a cracking or reforming
t heater to lower the temperature and arrest the cracking reaction.

finate

petroleum technology, the product from an extraction which is not
uble in the solvent, as contrasted with the extract.

ycle gas

as containing hydrocarbons which is being returned to the reaction
e for further processing.

Recycling

The procedure for recirculating a portion of the reactor product to the reactor for further processing. Unwanted by-products may be recycled to extinction.

Reduced crude

The bottoms or residual liquid from an atmospheric pipe still.

Reforming

Catalytic or thermal treatment of naphthas usually to obtain products of higher octane number.

Residual fuel oil

A petroleum product intended for combustion in large industrial installations composed principally of pitch and tar with end lighter oil added to give a product of satisfactory viscosity.

Residual stocks

Stocks remaining after certain light products are distilled off and spoken of as residual stocks.

Residue (residuum)

The material remaining as unevaporated liquid or solid from processes involving distillation or cracking.

Scrubbing

The process of removing an impurity from a petroleum product. For example, the removal of hydrogen sulfide from a hydrocarbon gas by scrubbing with sodium hydroxide solution.

Slack wax

The soft, crude paraffin that is obtained in a refinery from the processing of paraffin distillate.

Slop oil

Contaminated oil which has been recovered from a separator or other contaminated source. This oil must be redistilled before use in finished products.

ge

ge is used commonly in three separate senses – acid sludge, engine sludge, and tank sludge.

Acid sludge – A heavy, black, viscous, material of high specific gravity formed during the treatment of oils with sulfuric acid.

Engine sludge – The insoluble degradation product of lubricating oils and motor fuels, formed during their use in internal combustion engines and deposited from the oil on to engine parts outside combustion space.

Tank sludge – material which collects at the bottom of storage tanks. Such sludge usually contains a considerable amount of water.

ry

free-flowing mixture of solid and liquid; specifically, a suspension of cracking catalyst in cycle oil.

Smoke point

A measure of kerosine burning cleanliness. Using a standard laboratory lamp, it is expressed in terms of flame height in millimeters before smoking starts.

ker

In the thermal cracking process, a vertical cylindrical drum about four or five feet in diameter and forty feet high, designed for high pressure. This drum allows the hot oil to soak and react at a high temperature after leaving the coil. Most of the cracking occurs in this drum when it is used. In reference to thermal cracking, the expression 'coil only' means that no soaker is used.

Stabilizing

A process of promptly soda-washing petroleum fractions (especially from catalytic cracking) followed by adding inhibitor and air deaerating before any exposure to air to improve stability.

Stabilization

The removal from naphtha of the more volatile components (light hydrocarbons and H_2S) in order to hold the vapor pressure to a specified maximum.

Steam cracking

High temperature cracking of hydrocarbons in the presence of steam at low pressure.

Straight run

Synonym for virgin; an adjective applied to a petroleum distillate which has been fractionated from crude oil but changed in no other way.

Straight-run gasoline

A gasoline which is obtained directly from crude by fractional distillation.

Stripping

Substantially complete removal of the more volatile components from a mixture. Normally used to raise the flash point of kerosene, gas oil, or lubricating oil. It is usually accomplished by passing the cut from a flash drum or tower through a stripping vessel (or section) through which open steam or inert gas is passed, to sweep out the volatile components.

Tail

Term used in the petroleum industry for small amounts of relatively high-boiling material in a distillate oil of narrow boiling range, usually present because of poor fractionation.

Tail gas

The lightest hydrocarbon gas released from a refining process.

Tar

The bottoms product from any cracking operation. It is usually 12° A.P.I. gravity or less. It is not a virgin product. (See Pitch.)

Topped crude

Crude petroleum from which some of the lighter constituents have been removed by distillation.

ing

ough fractionation of crude petroleum usually to separate it into naphtha, heating oil, gas oil, and bottoms.

al feed

sum of the volume of oil pumped into a processing unit from various sources. It includes recycled products as well as fresh feed.

er cut

take a lower final boiling point on a stock than is normal, *e.g.*, fractionating a naphtha so that the 400-430° F. fraction is diverted to gasoline to heating oil in order to improve the volatility and the number of the gasoline fraction.

raforming

catalytic reforming process employing a platinum catalyst developed by the Standard Oil Co. (Indiana).

or phase cracking

cracking process in which the conditions of temperature and pressure are so chosen that the oil remains in the vapor state during the cracking reaction.

gin

petroleum distillate which has been fractionated from crude oil but changed in no other way.

cosity breaking (visbreaking)

thermal cracking process usually conducted at low cracking temperature (830°-870° F) to reduce the viscosity or pour point of a heavy oil.

ter white

grade of color for oils, defined as 21 in the Saybolt chromometer

Wax

Crystalline petroleum paraffin. Also any ester of a higher fatty acid with a higher (C_{16} - C_{30}) member of the alcohol series.

Wet gas

Natural gas that contains oil vapors in appreciable proportion, sometimes called 'casinghead gas'. Also gas from a process which contains readily condensable hydrocarbons.

White oils

General name applied to highly refined, colorless, hydrocarbon liquids of low volatility, and a wide range of viscosities. They are widely used for the lubrication of food and textile machinery and in medicine.

References

- MS. D. R. (1930) A study of the correlation between the biochemical and intraocular changes induced in rabbits by administration of naphthalene. *Brit. J. Ophthalmol.* 14: 545.
- IAN, E. D. (1953) Differentiation of olfactory receptors. *Proc. 4th Intern. Physiol. Congr.*, p. 151.
- Air over Louisville, Summary of a Joint Report.* (1958) Special Air Pollution Study of Louisville and Jefferson County, Kentucky, 1956-1957.
- I.A. Council on Industrial Health. (1956) Guiding principles of medical examinations in industry. *J. Am. Med. Assoc.*, 161: 975.
- I.A. Reference Committee on Hygiene, Public Health, and Industrial Health. (1957) *Proc. J. Am. Med. Assoc.*, 164: 1103.
- American Conference of Governmental Industrial Hygienists. (1959) Threshold Limit Values 1959. *A.M.A. Arch. Ind. Health*, 20: 66.
- I. *Toxicological Review, Xylene.* (1948) American Petroleum Institute, New York.
- I. *Toxicological Review, Toluene.* (1948) American Petroleum Institute, New York.
- I. *Toxicological Review, Naphthalene.* (1953) American Petroleum Institute, New York.
- ORF, M. L., and O'NEAL, M. J., JR. (1959) Mass spectrometric analyses of medium-viscosity lubricating oils. *Anal. Chem.*, 31: 164.
- SZO, E. (1958) Developments and recent trends in industrial medicine in Italy. *Med. Bull.* 18: 24.
- INAND, A., PAUFIQUE, L., and RODIER, J. (1947) Experimental intoxication with tetralin. *Arch. maladies profess. méd. travail et sécurité sociale*, 8: 124.

- BASILE, G. (1939) Sull'azione di alcuni prodotti di idrogeno della naftalina (tetralina e decalina) sul cristallino e membrane profonde oculari del coniglio. *Boll. Oculist.*, 18: 951.
- BATEMAN, E., and HENNINGSEN, C. (1923) Theory on the mechanism of protection of wood by preservatives. IV. Experimental hydrocarbons. *Proc. Am. Wood-Preservers' Assoc.*, 136.
- BÄTTIG, K., GRANDJEAN, E., and TURRIAN, V. (1956) Gesunde Menschen nach langdauernder Trimethylbenzol-Exposition. Malerwerkstatt. *Z. Prev.-Med.*, 1: 389.
- BÄTTIG, K., GRANDJEAN, E., ROSSI, L., and RICKENBACHER, J. (1956) Toxikologische Untersuchungen über Trimethylbenzol. *Gewerbepathol. Gewerbehyg.*, 16: 555.
- BENT, R. L., DESSLOCH, J. C., DUENNEBIER, F. C., FASSETT, G. L., GLASS, D. B., JAMES, T. H., JULIAN, D. B., RUBY, W. R., SMITH, M., STERNER, J. H., THIRTLE, J. R., VITTUM, P. W., and BERGER, A. (1951) Chemical constitution, electrochemical, spectrographic and allergenic properties of *p*-amino-*n*-dialkylbenzenes. *J. Am. Chem. Soc.*, 73: 3111.
- BERENBLUM, I., and SCHOENTAL, R. (1943) The metabolism of 1-methylbenzopyrene in mice and rats. I. The isolation of a hydroxyquinone derivative, and a consideration of their biological significance. *Cancer Research*, 3: 145.
- BERENBLUM, I., and SCHOENTAL, R. (1943a) The metabolism of 1-methyl-2-benzanthracene in mice and rats. *Cancer Research*, 3: 68.
- BERENBLUM, I., and SCHOENTAL, R. (1946) Metabolism of 3-methylbenzopyrene into 8- and 10-benzopyrenols in the animal body. *Cancer Research*, 6: 699.
- BERENBLUM, I., and SCHOENTAL, R. (1949) Metabolism of 1-methyl-2-benzanthracene. The isolation of 3-methoxychrysene by methylation of the principal metabolite of chrysene from rat feces. *Biochem. J.*, 44: 604.
- BERENBLUM, I., CROWFOOT, D., HOLIDAY, E. R., and SCHOENTAL, R. (1943) The metabolism of 3-methylbenzopyrene in mice and rats. The identification of the isolated products as 8-hydroxy-1-methylbenzopyrene and 3-methylbenzopyrene-5:8-quinone. *Cancer Research*, 3: 151.
- BERGMANN, E. D., and GRUENWALD, T. (1957) Paper chromatography of polycyclic aromatic hydrocarbons. *J. Appl. Chem. (London)*, 15.

- F. (1941) In what forms do rabbits excrete substances which contain a benzene ring condensed with a five-membered ring similar to the indole type? *Z. Physiol. Chem., Hoppe-Seyler's*, 269: 23.
- HITCH, M., and ELKINS, H. B. (1939) Chronic exposure to benzene (benzol). I. The industrial aspects. *J. Ind. Hyg. Toxicol.*, 321.
- AND, E. (1950) The biological significance of metabolism of cyclic compounds. *Biochemical Society Symposia No. 5*:40. *Biological Oxidation of Aromatic Rings*. Cambridge University Press, Great Britain.
- AND, E. (1958) The biological examination of carcinogenic substances. *Brit. Med. Bull.*, 14: 93.
- AND, E., and LEVI, A. A. (1935) Metabolism of polycyclic compounds. I. Production of dihydroxyanthracene from anthracene. *Biochem. J.*, 29: 2679.
- AND, E., and LEVI, A. A. (1936) Metabolism of polycyclic compounds. II. Production of dihydroxydihydroanthracene-turonic acid from anthracene. *Biochem. J.*, 30: 728.
- AND, E., and LEVI, A. A. (1936a) Metabolism of polycyclic compounds. III. Anthrylmercapturic acid. *Biochem. J.*, 30: 1225.
- AND, E., and WOLF, G. (1950) Metabolism of polycyclic compounds. 6. Conversion of phenanthrene into dihydroxydihydrophenanthrenes. *Biochem. J.*, 47: 64.
- CS. B. T., BOORD, C. E. and KURTZ, S. S. (1955) *Chemistry of petroleum hydrocarbons, Vol. II*, Reinhold Publishing Corporation, New York.
- CS. C. J. W., and YOUNG, L. (1956) Biochemical studies of toxicants. 9. The metabolic conversion of indene into *cis*- and *trans*-indane-1, 2-diol. *Biochem. J.*, 63: 264.
- ERON, G. R., and DONIGER, C. R. (1939) The toxicity of indene. *Pathol. Bacteriol.*, 49: 529.
- ERON, G. R., PATERSON, J. L. H., DESARAIN, G. S. W., and MAS, J. C. (1938) The toxicity of some methyl derivatives of benzene with special reference to pseudocumene and heavy coal naphtha. *J. Pathol. Bacteriol.*, 46: 95.
- OKI, A. (1942) Studio sperimentale sulla tossicità della tetralina e della decalina. *Med. lavoro*, 33: 145.

- CARLSON, G. W. (1946) Aplastic anemia following exposure to products of the sulfite-pulp industry: A report of one case. *Internal Med.*, 24: 277.
- CARPENTER, C. P., and SMYTH, H. F., JR. (1946) Chemical burn of the rabbit cornea. *Am. J. Ophthalmol.*, 29: 1363.
- CARPENTER, C. P., and SHAFFER, C. B., WEIL, C. S., and SMYTH, H. F., JR. (1944) Studies on the inhalation of 1,3-butadiene; with a comparison of its narcotic effect with benzol, toluol, and styrene and a note on the elimination of styrene by the human. *Ind. Hyg. Toxicol.*, 26: 69.
- CARPENTER, C. P., SMYTH, H. F., JR., and POZZANI, U. C. (1946) The assay of acute vapor toxicity, and the grading and interpretation of results on 96 chemical compounds. *Ind. Hyg. Toxicol.*, 28: 343.
- CHANG, L. H. (1943) The fecal excretion of polycyclic hydrocarbons following their administration to the rat. *J. Biol. Chem.*, 153: 171.
- CHANG, L. H., and YOUNG, L. (1943) Metabolism of Acenaphthene in the Rat. *J. Biol. Chem.*, 151: 87.
- CHARLET, E. M., LANNEAU, K. P., and JOHNSON, F. B., (1954) Analysis of gas oil and cycle stock from catalytic cracking. *Anal. Chem.*, 26: 861.
- CHASSEVANT, A., and GARNIER, M. (1903) Toxicité du Benzène et de quelques Hydrocarbures aromatiques homologues. *Compt. rend. Acad. soc. biol.*, 55: 1255.
- CHENOWETH, M. B. (1946) Ventricular fibrillation induced by hydrocarbons and epinephrine. *J. Ind. Hyg. Toxicol.*, 28: 151.
- CLEMENTS, G. R., and HILL, W. T. (1957) Preparation of tritiated 7,12-dimethylbenz(a)anthracene. *Science*, 125: 603.
- COGAN, D. G., and GRANT, W. M. (1945) An unusual type of keratitis associated with *n*-butyl alcohol. *Arch. Ophthalmol. (Chicago)*, 33: 106.
- COLICHMAN, E. L., and FISH, R. F. (1957) Resistance of terphenyls to heat and radiation. *Nucleonics* 15, No. 2: 72.
- CONCA, G. L., and MALTAGLIATI, A. (1955) Studio sull'assorbimento transcutaneo del benzolo. *Med. lavoro*, 46: 194.
- CORNER, E. D. S., and YOUNG, L. (1955) Biochemical studies of toxic agents. 8. 1,2-Dihydronaphthalene-1,2-diol and its role in the metabolism of naphthalene. *Biochem. J.*, 61: 132.

- SHIFFSKY, I., and WILLHITE, M. (1954) Metabolism of styrene in the rat. *J. Biol. Chem.*, 211: 549.
- CHMANN, W. B., and GERARDE, H. W. (1958) *Signs, Symptoms and Treatment of Certain Acute Intoxications*, C. C. Thomas, Springfield, Ill. U.S.A.
- CHMANN, W. B., and GERARDE, H. W. (1959) International symposium on maximum allowable concentrations of toxic substances in industry. *J. Occup. Med.*, 1: 463.
- CHMANN, W. B., KITZMILLER, K. V., DIERKER, M., and WITHEUP, S. (1947) Observations on the effects of diphenyl, *o*- and -aminodiphenyl, *o*- and *p*-nitrodiphenyl and dihydroxyoctachlorodiphenyl upon experimental animals. *J. Ind. Hyg. Toxicol.*, 29: 1.
- CKENS, F. (1945) 22nd. Rept. Brit. Emp. Cancer Campgn. p. 55.
- BRINER, K., RHOADS, C. P., and LAVIN, G. I., (1942) The spectroscopic study of biological extracts. II. The detection, isolation and biological effects on the metabolites of 1:2, 5:6-dibenzanthracene. *Cancer Research*, 2: 95.
- Dow Chemical Company (1950) *Health hazards and precautions for the safe handling and use of Dowtherm A*. Biochemical Research Department, Dow Chemical Co. Midland, Michigan.
- HAIZE, J. H., NELSON, A. A., WHITESELL, M. F., and ALVAREZ, E. (1946) *Toxicity of methylated naphthalene when topically applied to laboratory animals*. National Research Council, Insect Control Committee Report No. 183. Washington, D. C. p. 57.
- PIRE, F., and BOTQUIN, G. (1958) L'analyse qualitative et quantitative des huiles lourdes de goudron par chromatographie gazeuse. *Anal. Chim. Acta*, 18: 282.
- RHART, H. W., HEINRICH, R. L., LEWIS, W. E., NEWSON, T. M., WADLEY, E. F. (1959) Manufacture and utilization of aromatics from petroleum. *World Petrol. Congr., Proc., 5th Congr., Sect. IV., Paper 1*.
- Y, L. T., PRIESTLEY, W., Jr., REHNER, J. J., and HALL, M. E. (1953) Properties of high boiling petroleum products. Non-biological laboratory methods for predicting carcinogenicity. *Anal. Chem.*, 25: 1500.
- KARDT, R. E. (1959) *Industrial Carcinogens*, Grune and Stratton, New York.
- NER, E. (1924) Über Hautentzündungen infolge Naphthalinhalgen Schmieröles. *Zentr. Gewerbehyg. Unfallverhüt.*, 1: 20.

- ELKINS, H. B. (1959) *The Chemistry of Industrial Toxicology*, 2nd John Wiley and Sons, New York.
- ELKINS, H. B., and PAGNOTTO, L. D. (1956) Benzene content petroleum solvents. *A.M.A. Arch. Ind. Health*, 13: 51.
- EL MASRI, A. M., SMITH, J. N., and WILLIAMS, R. T. (1958) Studies in detoxication. 73. The metabolism of alkylbenzenes: Phenylacetylene and phenylethylene (Styrene). *Biochem. J.*, 68: 199.
- EL MASRY, A. M., SMITH, J. N., and WILLIAMS, R. T. (1956) Studies in detoxication. 69. The metabolism of alkylbenzenes; *n*-propylbenzene and *n*-butylbenzene with further observations on ethylbenzene. *Biochem. J.*, 64: 50.
- ELSON, L. A., GOULDEN F., and WARREN, F. L. (1945) Urinary partition of sulfur in rats treated with aromatic hydrocarbons with special reference to growth retardation. *Biochem. J.*, 39: 301.
- FABRE, R., and TRUHAUT, R. (1954) *Le problème des solvants de remplacement du benzène dans ses rapports avec l'hygiène industrielle*. Congresso Internazionale de Medicina del Lavoro, Napoli.
- FABRE, R., TRUHAUT, R., LAHAM, S., et PERSON, M. (1955) Recherches toxicologiques sur les solvants de remplacement de benzène. Etude du toluène. *Arch. maladies profess. méd. travail et sécurité sociale*, 16: 197.
- FABRE, R., TRUHAUT, R., BERNUCHON, J., et LOISILLIER, F. (1955) Recherches toxicologiques sur les solvants de remplacement de benzène III. Etude de l'isopropylbenzène ou cumène. *Arch. maladies profess. méd. travail et sécurité sociale*, 16: 288.
- FISCHER, H. G. M., PRIESTLEY, W., EBY, L. T., WANLESS, G. C., and REHNER, J., JR. (1951) Properties of high boiling petroleum products. *A.M.A. Arch. Ind. Hyg. Occupational Med.*, 4: 315.
- FITZHUGH, O. G., and BUSCHKE, W. H. (1949) Production of cataracts in rats by β -tetralol and other naphthalene derivatives. *A.M.A. Arch. Ophthalmol.*, 41: 572.
- GADSDEN, R. H., MELLETTE, R. R., and MILLER, W. C., JR. (1955) Scrap iron intoxication. *J. Am. Med. Assoc.*, 168: 1220.
- GALEWSKY, S. (1922) Über Dermatitiden durch Terpentinersatz. *Dermatol. Wochenschr.*, 1922 I: 1080.
- GERARDE, H. W. (1956) Toxicological studies on hydrocarbons. A method for the quantitative collection of femoral marrow from small laboratory animals. *A.M.A. Arch. Ind. Health*, 13: 331.

- GERARDE, H. W. (1959) Toxicological studies on hydrocarbons. III. The biochemorphology of the phenylalkanes and phenylalkenes. *A.M.A. Arch. Ind. Health*, 19: 403.
- GERARDE, H. W. (1959a) Toxicological studies on hydrocarbons. V. Kerosine. *Toxicol. and Appl. Pharmacol.*, 1: 462.
- GERARDE, H. W. (1959b) La toxicologica y bioquimica de los hidrocarburos aromaticos monociclicos. *Segunda Conferencia Inter-Americana de Medicina del Trabajo*. Coral Gables, Florida.
- LETTI, G., and MARIANI, L. (1956) Eye changes due to naphthalene. *Med. lavoro*, 47: 533.
- LIDMANN, H. (1929) Experimentelle Supranukleärkatarakt und Kernsklerose. *Klin. Monatsbl. Augenheilk.*, 83: 433.
- ORDON, H. T., and HURAUX, M. J. (1959) Spot tests for aromatic compounds using 2,4,7-trinitrofluorenone. *Anal. Chem.* 31: 303.
- FEENBURG, L., MAYERS, M. R., GOLDWATER, L., and SMITH, A. R. (1939) Benzene (benzol) poisoning in the rotogravure printing industry in New York City. *J. Ind. Hyg. Toxicol.* 21: 395.
- IMES, A. J., and YOUNG, L., (1956) The metabolism of 2-methylnaphthalene. *Biochem. J.*, 62: 11p.
- MERTIN, D. L. and GERARDE, H. W. (1959) Toxicological studies on hydrocarbons IV. A method for the quantitative determination of benzene and certain alkylbenzenes in blood. *A.M.A. Arch. Ind. Health*, 20: 262.
- ADDOW, A. (1958) Chemical carcinogens and their modes of action. *Brit. Med. Bull.*, 14: No. 2, 79.
- ENSEN, N., and GROVES, D. (1959) Aromatics in trouble. *Chem. Week*, 84: 53, March 7.
- PERPER, K. H. (1957) The metabolism of pyrene. *Brit. J. Cancer*, 11: 199.
- PERPER, K. H. (1958) The intermediary metabolism of pyrene. *Brit. J. Cancer*, 12: 116.
- ERRILLS, J. M., and HUGHES, T. F. (1958) Enumeration of the 'crayings' of some pregnant women. *Brit. Med. J.*, 11: 39.
- RTWELL, J. L. (1951) *Survey of compounds which have been tested for carcinogenic activity*. 2nd Ed. Federal Security Agency, Public Health Service Pub. No. 149, U. S. Gov't. Printing Off. Washington, D. C.
- LEVY, J. M. (1942) *University Queensland Papers.*, Chem. Dept., 7, No. 23.

- HAYNES, W. (1936) *Men, Money and Molecules*. Doubleday, and Co., Inc. Garden City, New York.
- HENDRICKSON, J. G., and WADSWORTH, F. T. (1958) Synthesis of p-xylene from pseudocumene. *Ind. Eng. Chem.*, 50: 877.
- HINE, C. H., UNGAR, H., ANDERSON, H. H., KODAMA, J. K., CLOW, J. K., JACOBSEN, N. W. (1954) Toxicological studies on p-xylene. *A.M.A. Arch. Ind. Hyg. Occupational Med.*, 1: 1-10.
- HIRSCH, S. (1932) Concerning the effect of chronic xylene poisoning. *Verhandl. deut. Ges. inn. Med.*, 44: 486.
- HODGE, H. C., and STERNER, J. H. (1943) Tabulation of toxic effects of xylene. *Am. Ind. Hyg. Assoc. Quart.*, 10: 93.
- HOLT, J. P., HENDRICKS, N. V., ECKARDT, R. E., STANTON, J. W., and PAGE, R. C. (1951) A cancer-control program for high boiling catalytically cracked oils. *A.M.A. Arch. Ind. Hyg. and Occupational Med.*, 4: 325.
- HUEPER, W. C. (1942) *Occupational Tumors and Allied Diseases*. C. C. Thomas, Springfield, Ill., p. 189-192.
- HULTGREN, G. (1926) Action de différents benzols méthylés sur la composition du sang du lapin. *Compt. rend. soc. Sci. Paris*, 273: 1066.
- JOST, H., (1932) Urinalyses in chronic poisoning by benzene and benzene derivatives. *Arch. Gewerbepathol. Gewerbehyg.*, 3: 1-10.
- KATZEN, R. (1958) Watch petrochemicals grow in Europe. *Petroleum Refiner* 37, No. 11: 171.
- KENNAWAY, E. L. (1924) Cancer-producing tars and tar fractions. *J. Ind. Hyg.* 5: 462.
- KLONTZ, C. (1953) Personal communication.
- KNOOP, F., and GEHRKE, M. (1925) The oxidation of acetic acid, acetone and toluene. *Z. physiol. Chem.*, 146: 63.
- KOELSCH, F. (1926) Vergiftungen. Aliphatische Verbindungen. *Hb. soz. Hyg.*, 2: 390.
- KURATSUNE, M., and HUEPER, W. C. (1958) Polycyclic aromatic hydrocarbons in coffee soots. *J. Natl. Cancer Inst.*, 20: 37.
- KUSCHNER, M., LASKIN, S., CRISTOFANO, E., and NELSON, H. (1958) *Experimental Carcinoma of the Lung*. Proc. Third National Cancer Conference. Am. Cancer Soc., New York, p. 485.
- LAZAREW, N. V. (1929) Toxicity of various hydrocarbon vapors. *Exptl. Pathol. and Pharmacol.*, Naunyn-Schmiedeberg's, 143: 1-10.

- MAN, K. B., and FLURY, F. (1943) *Toxicology and Hygiene of Industrial Solvents*. Translated by E. King and H. F. Smyth, Jr. Williams and Wilkins Co., Baltimore, Md.
- ER, J., ed. (1958) Cancer chemotherapy screening, data I. *Cancer research*, 18: No. 8: part 2.
- ER, J., ed (1959) Cancer chemotherapy screening, data II. *Cancer research*, 19: No. 3: part 2.
- ENZ, E., and SHEAR, M. J. (1936) Studies in carcinogenesis. II. The detection of dibenzanthracene in mouse tumors induced by this hydrocarbon. *Am. J. Cancer*, 26: 333.
- NS, M. J. (1959) Vehicular exhausts: Identification of further carcinogens of the polycyclic aromatic hydrocarbon class. *Brit. J. Cancer*, 13: 126.
- NS, M. J. and JOHNSTON, H. (1957) Aromatic hydrocarbons from vehicular exhausts. *Brit. J. Cancer*, 11: 60.
- LAUGHLIN, R. S. (1946) Chemical burns of the human cornea. *Am. J. Ophthalmol.*, 29: 1355.
- KELL, J. V., RIEDERS, F., BRIEGER, H., and Bauer, E. L. (1951) Acute hemolytic anemia due to ingestion of naphthalene moth balls. *Pediatrics*, 7: 722.
- FETT, P. A. DOHERTY, T. F., and MONKMAN, J. L. (1956) A direct method for the collection and determination of micro amounts of benzene or toluene in air. *Am. Ind. Hyg. Assoc. Quart.*, 17: 186.
- LAN, I. (1957) *Handbook of Solvents. Vol. I., Pure Hydrocarbons*. Reinhold Publ. Corp., New York.
- ER, S. (1920) Über Schädigung der hämatopoetischen Organe durch Naphthalin. *Klin. Wochenschr.*, 57: 1025.
- AM, S. R., WOLF, J. T., and SHERWIN, C. P. (1927) Comparative metabolism of certain aromatic acids. XII. Fate of triphenylacetic acid also triphenylmethane and triphenylcarbinol in the animal body. *J. Biol. Chem.* 71: 695.
- AMATO, Y. (1938) On the effect of benzene derivatives on the blood picture and various other organs. *Zentr. Gewerbehyg. Unfallverhüt.*, 25: 70.
- ER, J. (1958) An odor evaluation apparatus for field and laboratory use. *Am. Ind. Hyg. Assoc. J.*, 19: 1.
- H, W. J. P. (1948) Metabolism of fluorene in the rabbit. *Biochem.*, 43: 533.

- NELSON, F. C. and FIERO, G. W. (1954) A selected aromatic fraction naturally occurring in petroleum as a pesticide solvent. *J. Food Chem.*, 2: 735.
- Occupation and Health* (1930) *An encyclopaedia of hygiene, pathology and social welfare*. Vol. 1., International Labour Office, Geneva.
- ÖVRUM, P. (1956) Determination of atmospheric benzene concentration by displacement following adsorption on silica gel. *Br. Ind. Med.*, 13: 210.
- PATTY, F. (1949) *Industrial Hygiene and Toxicology*, Vol. II. Interscience Publishers Inc., New York.
- PECCHIAI, L., and SAFFIOTTI, U., (1957) Studio della tossicità del difenile, dell'ossidifenile e della loro miscela ('Dowtherm'). *Med. lavoro*, 48: 247.
- PÉRONNET, M. (1935) Experimental poisoning by benzene vapor. Concentration of benzene in the blood, and speed of its disappearance. *J. pharm. chim.*, 21: 503.
- Pfizer Spectrum (1956), *Naphthalene poisoning in children*.
- POHL, J. and RAWICZ, M. (1919) Über das Schicksal des Tetrahydronaphtalins (Tetralin) in Tierkörper. *Z. physiol. chem.*, 104: 95.
- ROBINSON, D., and WILLIAMS, R. T. (1955) Studies in detoxication 61. The metabolism of alkylbenzenes, *tert*-butylbenzene. *Biochem. J.*, 59: 159.
- ROBINSON, D., SMITH, J. N., and WILLIAMS, R. T. (1955) Studies in detoxication 60. The metabolism of alkylbenzenes isopropylbenzene (cumene) and derivatives of hydratropic acid. *Biochem. J.*, 59: 153.
- ROCKEMANN, W. (1922) Über Tetralinharn. *Arch. Exptl. Path. Pharmacol.*, Naunyn-Schmiedeberg's, 92: 52.
- ROGERS, J. C., and HOOPER, C. C. (1957) MAC for styrene. *Ind. Med. Surg.*, 26: 32.
- ROSSI, L., and GRANDJEAN, E. (1957) L'eliminazione urinaria dei fenoli in animali esposti al trimetilbenzoli. *Med. lavoro*, 48: 52.
- ROSSINI, F. D., MAIR, B. J., and STREIFF, A. J. (1954) *Hydrocarbons from petroleum*. ACS Monograph 121. Reinhold Publ. Co., N. Y. p. 362-72.
- ROWE, V. K., ATCHISON, G. J., LUCE, E. N., and ADAMS, E. M. (1957) The determination of monomeric styrene in air. *J. Ind. Hyg. Toxicol.*, 25: 348.

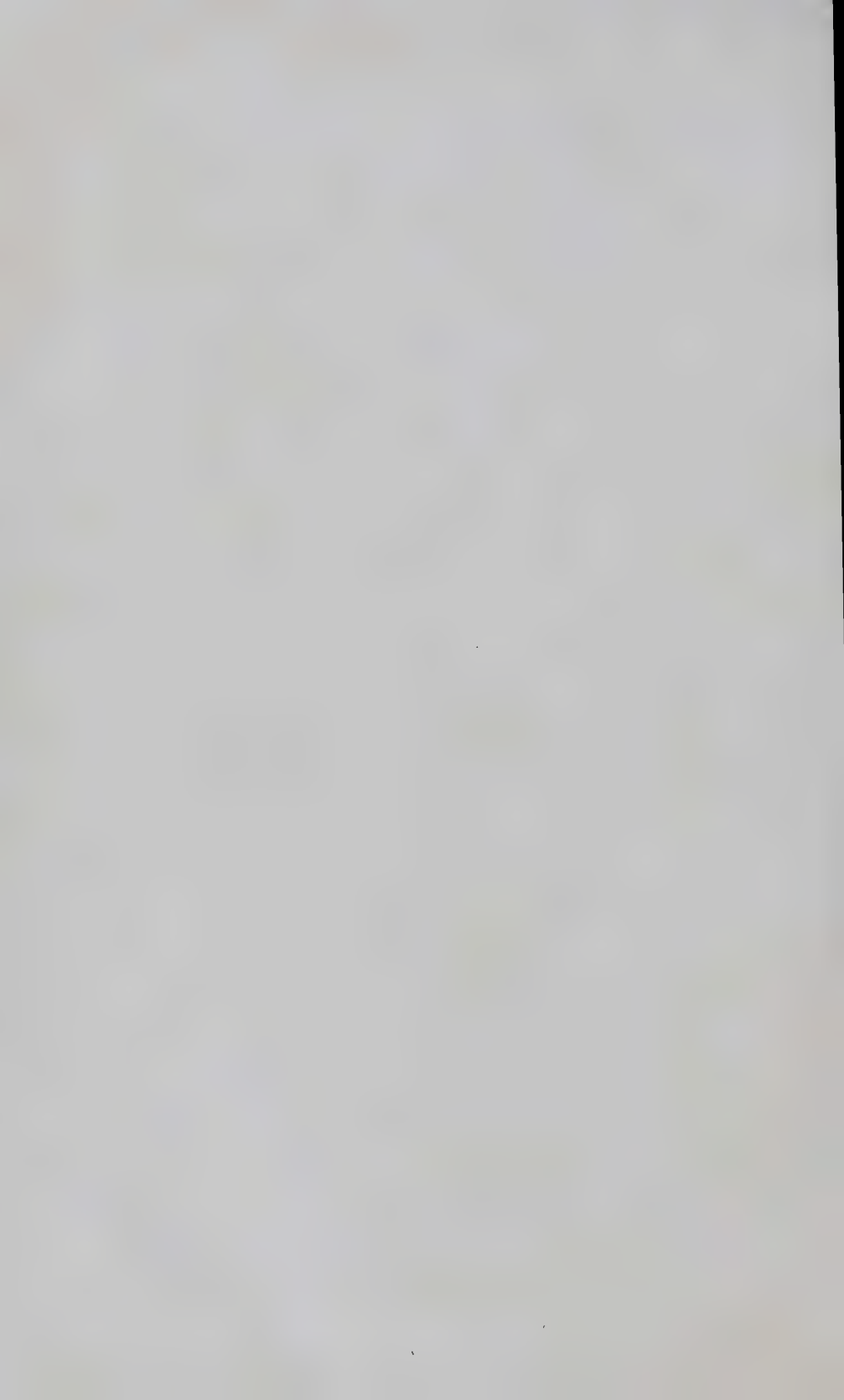
- ICKI, E., MILLER, R., STANLEY, T., and HAUSER, T. (1958) Detection of polynuclear hydrocarbons and phenols with benzol and peronal chlorides. *Anal. Chem.*, 30: 1130.
- ICKI, E., STANLEY, T., HAUSER, T. R., and TAFT, R. A. (1959) Ultraviolet, visible and fluorescent spectral analysis of polynuclear hydrocarbons. In *Abstracts of Papers 136th meeting, Am. Chem. Soc.* Div. of Water, Sewage and Sanitation Chem.
- MID, E. (1956) Diseases of the cornea in furniture polishers. *Arch. Gewerbepathol. Gewerbehyg.*, 15: 37.
- RENK, H. H. (1955) Pitfalls in using maximum allowable concentrations in air pollution. *Am. Ind. Hyg. Assoc. Quart.*, 16: 30.
- TT, J. L., CARTWRIGHT, G. E., and WINTROBE, M. M. (1959) Acquired aplastic anemia: An analysis of thirty-nine cases and review of the pertinent literature. *Medicine*, 38: 119.
- BIK, P., and DELLA PORTA, G. (1957) Carcinogenesis and acute toxication with large doses of polycyclic hydrocarbons. *A.M.A. Arch. Pathol.*, 64: 691.
- BIK, P., and HARTWELL, J. L. (1957) *Survey of compounds which have been tested for carcinogenic activity. Supplement I.* U.S. Department of Health, Education, and Welfare. Public Health Service Publication No. 149, Suppl. I, U.S. Government Printing Off., Washington, D. C.
- ERMAN, L., and SHIDELER, M. E. (1958) Determination of bi-naphenyl in the presence of polyphenyls. Water solubility method. *Anal. Chim. Acta*, 18: 540.
- LIANSKI, S. B. (1959) *Establishment of Standard Hygienic Orders with reference to Maximum Allowable Concentrations of toxic substances in the air of workrooms.* Prescribed at the International Congress on Occupational Health, Helsinki, Finland.
- TH, H. P., and WHIPPLE, H. G. (1930) Bile salt metabolism. VII. Indene, hydrindene and isatin. *J. Biol. Chem.*, 89: 719.
- TH, W. E., SUNDERLAND, D. A., and SUGIURA, K. (1951) Experimental analysis of the carcinogenic activity of certain petroleum products. *A.M.A. Arch. Ind. Hyg. Occupational Med.*, 4: 299.
- TH, H. F. JR., CARPENTER, C. P., and WEIL, C. S. (1951) Ranged toxicity data: List IV. *A.M.A. Arch. Ind. Hyg. Occupational Med.*, 4: 119.

- SMYTH, H. F., JR. (1956) Improved communication. Hyg standards for daily inhalation. *Am. Ind. Hyg. Assoc. Quart.*, 17: 17.
- SOLLMANN, T. (1957) *A. Manual of Pharmacology*, 8th Ed., W. B. Saunders Co., Philadelphia, Pennsylvania.
- SPECTOR, W. S. (1956) *Handbook of Toxicology, Vol. I.*, W. B. Saunders Co., Philadelphia, Pennsylvania.
- SPENCER, H. C., and IRISH, D. D., ADAMS, E. M., and ROWE, V. (1942) The response of laboratory animals to monomeric styrene. *J. Ind. Hyg. Tox.*, 24: 295.
- STEKOL, J. A. (1937) Mercapturic acid synthesis in animals. V. effect of naphthalene on the growth of rats as related to diet varying sulfur content. *J. Biol. Chem.*, 121: 87.
- STOCK, C. C., ed. (1953) Negative data from experimental carcinoma chemotherapy studies. *Cancer Research, Supp. 1.*
- STOCK, C. C., ed. (1955) Negative data from experimental carcinoma chemotherapy studies, II. *Cancer Research, Supp. 2.*
- STROUD, S. W. (1939) Preliminary investigation of the metabolism of stilbene. *Nature*, 144: 245.
- STROUD, S. W. (1940) The metabolism of the parent compounds and some of the simpler synthetic estrogenic hydrocarbons. *J. Endocrinol.*, 2: 55.
- SUNDERLAND, D. A., SMITH, W. E., and SUGIURA, K. (1951) The pathology and growth behavior of experimental tumors induced by certain petroleum products. *Cancer*, 4: 1232.
- SVIRBELY, J. L., DUNN, R. C., and VON OETTINGEN, W. F. (1946) The acute toxicity of vapors of certain solvents containing appreciable amounts of benzene and toluene. *Ind. Hyg. Toxicol.*, 25: 3.
- SVIRBELY, J. L., DUNN, J. E., DUNN, R. C., ALFORD, W. C., SIMMONS, C. G., PETERSON, D. C., VON OETTINGEN, W. F., and NELSON, P. A. (1946) *Report on an appraisal of the toxicity and potential dangers of solvents consisting essentially of methylated naphthalene derivatives to be used as solvents for DDT in insecticidal mixtures*. National Research Council, Insect Control Committee Report No. 183. Washington, D. C. p. 10.
- TEISINGER, J., and BERGEROVÁ-FIŠEROVÁ, V. (1955) Valeur comparative de la détermination des sulfates et du phénol contenus dans l'urine pour l'évaluation de la concentration du benzène dans l'air. *Arch. maladies profess. méd. travail et sécurité sociale*, 16: 2.

- INGER, J., and SRBOVÁ, J. (1955) L'élimination de l'acide benzoïque dans l'urine et son rapport avec la concentration maximum tolérable de toluène dans l'air. *Arch. maladies profess. méd. travail sécurité sociale*, 16: 216 .
- OMAS, J. R., TALBENS, B. D., SANBORN, E. N., and CRIPPS, J. (1959) Fluorescent spectra of aromatic hydrocarbons found in polluted atmospheres. In *Abstracts of Papers 136th Meeting, Am. chem. Soc., Div. of Water, Sewage and Sanitation Chemistry*.
- ORPE, W. V. (1950) The metabolism of foreign organic compounds. *Brit. Sci. News*, 3: 78.
- Occupational Eye Hazards* (1949) Pub. No. 494. National Society for the Prevention of Blindness, Inc., New York.
- EFFERT, L. (1952) Le dosage colorimétrique de traces de benzène dans le sang et dans l'air. *Ann. fals. et fraudes*, 45: 181.
- IGAR, H., HINE, C. H., KODAMA, J. K., and ANDERSON, H. H. (1955) Neuropathology of rats experimentally poisoned with *p*-tert-butyltoluene. *A.M.A. Arch. Pathol.*, 60: 139.
- K. Department of Scientific and Industrial Research (1950) *Methods for the detection of toxic gases in industry. Leaflet No. 4: Benzene Vapour*. H. M. Stationary Office, London.
- S. Steel (1958) *Age of Coal Chemicals*.
- S. Tariff Commission (1958) *Synthetic Organic Chemicals*. U. S. Production and Sales, 1957, Report No. 203, 2nd Series. U. S. Gov't. Printing Off. Washington, D. C.
- ETTE, G., and CAVIER, R. (1954) Percutaneous absorption and chemical constitution. Hydrocarbons, alcohols and esters. *Arch. intern. Pharmacodynamie*, 97: 232.
- N DUUREN, B. L. (1958) The polynuclear aromatic hydrocarbons in cigarette smoke condensate. II. *J. Natl. Cancer Inst.*, 21: 623.
- N OETTINGEN, W. F. (1940) *Toxicity and potential dangers of aliphatic and aromatic hydrocarbons; a critical review of the literature*. Federal Security Agency, U. S. Public Health Service. Public Health Bulletin No. 255. U. S. Gov't. Printing Off. Washington, D.C.
- N OETTINGEN, W. F., NEAL, P. A., and DONAHUE, D. D. (1942) The toxicology and potential dangers of toluene. *J. Am. Med. Assoc.*, 118: 579.
- NESS, G. G., EBY, L. T., and REHNER, J. (1951) Properties of high boiling petroleum products. *Anal. Chem.*, 23: 563.

- WEDGWOOD, P., and COOPER, R. L. (1956) Detection and determination of traces of polynuclear hydrocarbons in industrial effluents and sewage. IV. The quantitative examination of effluents. *Anal. Chem.*, 28: 42.
- WEIGERT, F., CALCUTT, G., and POWELL, A. K. (1947) The course of the metabolism of benzpyrene in the skin of the mouse. *Br. J. Cancer*, 1: 405.
- WEIL-MALHERBE, H. (1946) The solubilization of polycyclic aromatic hydrocarbons by purines. *Biochem. J.*, 40: 351.
- WERNER, H. W., DUNN, R. C., and VON OETTINGEN, W. F. (1956) The acute effects of cumene vapors in mice. *J. Ind. Hyg. Toxicol.*, 26: 264.
- WEST, H. D., and JEFFERSON, N. C. (1942) The effect of aromatic hydrocarbons on the growth of young rats. *J. Nutrition*, 23: 4.
- WEST, H. D., LAWSON, J. R., MILLER, I. H., and MATHURA, G. (1956) The fate of diphenyl in the rat. *Arch. Biochem. Biophys.*, 54: 14.
- WHELAND, G. W. (1949) *Advanced Organic Chemistry*. John Wiley and Sons, Inc., New York.
- WHITE, R. P. (1934) *The dermatergoses or occupational affections of the skin, giving descriptions of the trade processes, the responsible agents and their actions*. H. K. Lewis and Co., London.
- WIEST, W. G., and HEIDELBERGER, C. (1953) The interaction of carcinogenic hydrocarbons with tissue constituents. II. 1:2,5:6-Dibenzanthracene-9,10-¹⁴C in skin. *Cancer Research*, 13: 250.
- WILLIAMS, R. T. (1947) *Detoxication mechanisms; the metabolism of drugs and allied organic compounds*. John Wiley & Sons, New York.
- WILLIAMS, R. T., and ROBINSON, D. (1955) Studies in detoxication. 61. The metabolism of alkylbenzenes, *tert*-butylbenzene. *Biochem. J.*, 59: 159.
- WINTROBE, M. M. (1946) *Clinical Hematology*. Lea & Febiger, Philadelphia, Pa. p. 120.
- WOERMLEY, D. L. (1954) Magnetic susceptibility data for some biologically important derivatives of phenanthrene. *Arch. Biochem. Biophys.*, 50: 199.
- WOLF, M. A., ROWE, V. K., MCCOLLISTER, D. D., HOLLINGSWORTH, R. L., and OYEN, F. (1956) Toxicological studies of certain alkylated benzenes and benzene. *A.M.A. Arch. Ind. Health*, 14: 387.

- RONOW, A. (1929) Morphological changes of the blood under influence of benzene and its derivatives. *Arch. Pathol. Anat. u. Physiol., Virchow's*, 271: 173.
- ST, W. P., SCHRENK, H. H., WAITE, C. P., and PATTY, F. A. (1930) Acute response of guinea pigs to vapors of some new commercial organic compounds. II. Ethylbenzene. *Public Health Repts. (U.S.)*, 5: 1241.
- ST, W. P., SCHRENK, H. H., and MAUTZ, P. H. (1935) Procedure for the removal and determination of small amounts of benzene in biological materials. *U.S. Bur. Mines, Rept. Invest., No. 3282*.
- ST, W. P., PEARCE, S. J., and SCHRENK, H. H. (1936) A microcoulometric method for the determination of toluene. *U. S. Bur. Mines, Rept. Invest., No. 3323*.
- NG, L. (1950). *Symp. Biochem. Soc.* 5: 29.
- GLER, E. (1873) On the behavior of camphor cymol in the animal organism. *Arch. Exptl. Pathol. Pharmacol., Naunyn-Schmiedeberg's*, 63.
- KHAM, W. H., and CHILDS, B. (1958) A defect of glutathione metabolism in erythrocytes from patients with naphthalene-induced hemolytic anemia. *Pediatrics*, 22: 461.
- LZER, W. W., and APT, L. (1949) Acute hemolytic anemia due to naphthalene poisoning; a clinical and experimental study. *J. Am. Med. Assoc.*, 141: 185.



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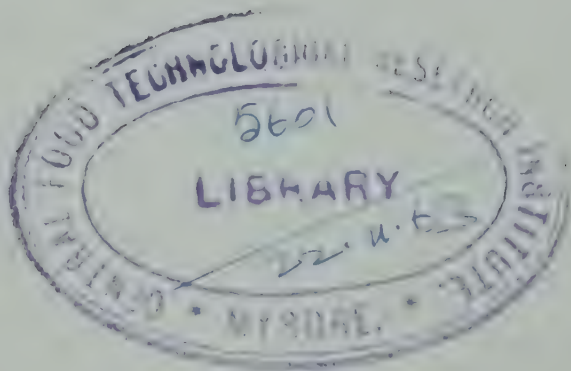
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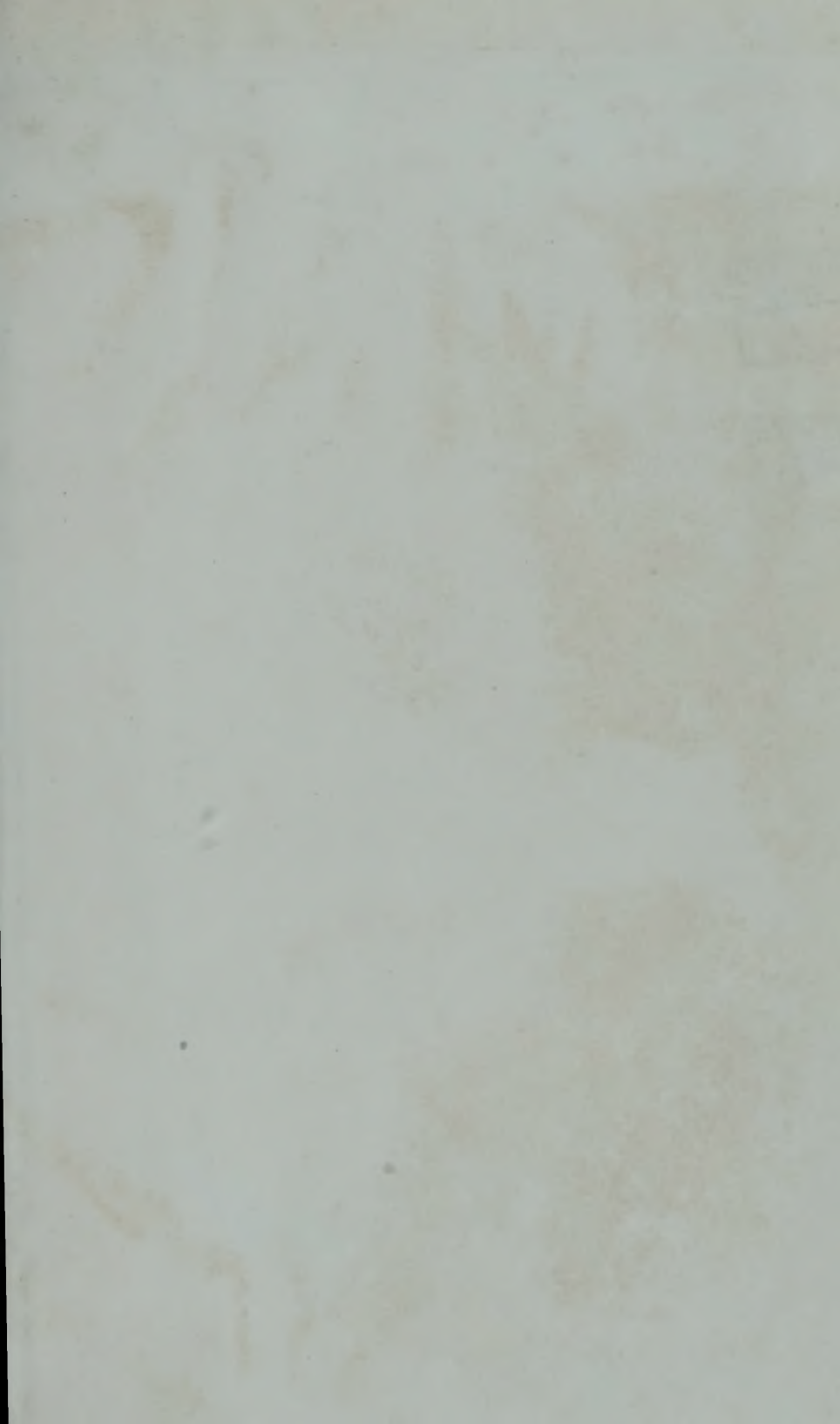
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